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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 213/81, A61K 31/44 — A1

(11) International Publication Number: WO 91/18883

(43) International Publication Date: 12 December 1991 (12.12.91)

(21) International Application Number: PCT/US91/03940

(22) International Filing Date: 5 June 1991 (05.06.91)

(30) Priority data:
534,387 7 June 1990 (07.06.90) US

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Patents-U.S., UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406 (US).

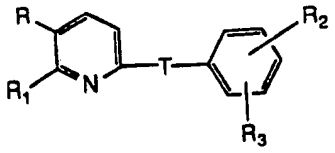
(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : DAINES, Robert, A. [US/US]; 107 North Stone Ridge Drive, Lansdale, PA 19446 (US). KINGSBURY, William, Dennis [US/US]; 865 Babb Circle, Wayne, PA 19087 (US).

(74) Agents: KANAGY, James, M. et al.; SmithKline Beecham Corporation, Corporate Patents-U.S., UW2220, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), US.

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: AMIDE LINKED PYRIDYLE-BENZOIC ACID DERIVATIVES FOR TREATING LEUKOTRIENE-RELATED DISEASES



(I)

(57) Abstract

This invention relates to compounds of formula (I), where T is an amide linkage and the R groups are defined herein. These compounds are useful as leukotriene antagonists.

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Amide Linked Pyridyl-Benzoic Acid Derivatives For Treating Leukotriene-related Diseases

Scope of the Invention

This invention relates to amide linked pyridyl-benzoic acid derivatives which are useful for treating diseases associated with leukotrienes. These compounds are particularly useful in treating diseases attributable to hydroxyleukotrienes, especially LTB_4 and LTB_4-agonist active substances.

Background of the Invention

The family of bioactive lipids known as the leukotrienes exert pharmacological effects on respiratory, cardiovascular and gastrointestinal systems. The leukotrienes are generally divided into two sub-classes, the peptidoleukotrienes (leukotrienes C_4, D_4 and E_4) and the hydroxyleukotrienes (leukotriene B_4). This invention is primarily concerned with the hydroxyleukotrienes (LTB) but is not limited to this specific group of leukotrienes.

The peptidoleukotrienes are implicated in the biological response associated with the "Slow Reacting Substance of Anaphylaxis" (SRS-A). This response is expressed *in vivo* as prolonged bronchoconstriction, in cardiovascular effects such as coronary artery vasoconstriction and numerous other biological responses. The pharmacology of the peptidoleukotrienes include smooth muscle contractions, myocardial depression, increased vascular permeability and increased mucous production.

By comparison, LTB_4 exerts its biological effects through stimulation of leukocyte and lymphocyte functions. It stimulates chemotaxis, chemokinesis and aggregation of polymorphonuclear leukocytes (PMNs).

They are critically involved in mediating many types of cardiovascular, pulmonary, dermatological, renal, allergic, and inflammatory diseases including asthma, adult respiratory distress syndrome, cystic fibrosis, psoriasis, and inflammatory bowel disease.

Leukotriene B_4 (LTB_4) was first described by Borgeat and Samuelsson in 1979, and later shown by Corey and co-workers to be 5(S),12(R)-dihydroxy-(Z,E,E,Z)-6,8,10,14-eicosatetraenoic acid.

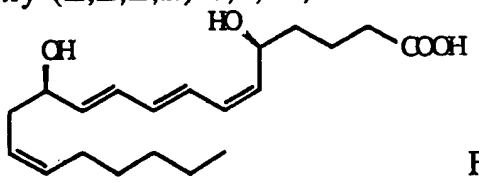


Fig. I

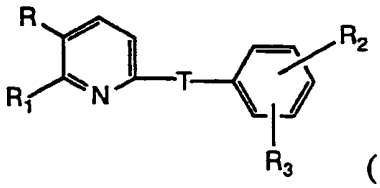
It is a product of the arachidonic acid cascade that results from the enzymatic hydrolysis of LTA4. It has been found to be produced by mast cells, polymorphonuclear leukocytes, monocytes and macrophages. LTB4 has been shown to be a potent stimulus *in vivo* for PMN leukocytes, causing increased chemotactic and chemokinetic migration, adherence, aggregation, degranulation, superoxide production and cytotoxicity. The effects of LTB4 are mediated through distinct receptor sites on the leukocyte cell surface which exhibit a high degree of stereospecificity. Pharmacological studies on human blood PMN leukocytes indicate the presence of two classes of LTB4-specific receptors that are separate from receptors specific for the peptide chemotactic factors. Each of the sets of receptors appear to be coupled to a separate set of PMN leukocyte functions. Calcium mobilization is involved in both mechanisms.

LTB4 has been established as an inflammatory mediator *in vivo*. It has also been associated with airway hyper responsiveness in the dog as well as being found in increased levels in lung lavages from humans with severe pulmonary dysfunction.

By antagonizing the effects of LTB4, or other pharmacologically active mediators at the end organ, for example airway smooth muscle, the compounds and pharmaceutical compositions of the instant invention are valuable in the treatment of diseases in subjects, including human or animals, in which leukotrienes are a factor. Some of these compounds may also inhibit the 5-lipoxygenase enzyme or may be LTD_4 antagonists.

SUMMARY OF THE INVENTION

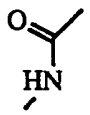
The compounds of this invention are represented by formula (I)



(I)

or a pharmaceutically acceptable salt or N-oxide thereof where

T is the amide linking group



where the carbonyl carbon is bonded to the pyridyl ring;

R is C_1 to C_{20}-aliphatic, unsubstituted or substituted phenyl C_1 to C_{10}-aliphatic where substituted phenyl has one or more radicals selected from the group consisting of lower alkoxy, lower alkyl, trihalomethyl, or halo, or R is C_1 to C_{20}-aliphatic-O-, or R is unsubstituted or substituted phenyl C_1 to C_{10}-aliphatic-O- where substituted phenyl has one or more radicals which are lower alkoxy, lower alkyl, trihalomethyl, or halo;

R_1 is R_4, -(C_1 to C_5 aliphatic)R_4, -(C_1 to C_5 aliphatic)CHO, -(C_1 to C_5 aliphatic)CH_2OR_8, -CH_2OH or -CHO;

R_2 is hydrogen, -COR_5 where R_5 is -OH, a pharmaceutically acceptable ester-forming group -OR_6, or -OX where X is a pharmaceutically acceptable cation, or R_5 is -$N(R_7)_2$ where R_7 is H, or an aliphatic group of 1 to 10 carbon atoms, a cycloalkyl-$(CH_2)_n$- group of 4 to 10 carbons where n is 0-3 or both R_7 groups combine to form a ring having 4 to 6 carbons, or R_2 is $NHSO_2R_9$ where R_9 is -CF_3, C_1 to C_6 alkyl or phenyl;

R_3 is hydrogen, lower alkoxy, halo, -CN, COR_5, or OH;

R_4 is -COR_5 where R_5 is -OH, a pharmaceutically acceptable ester-forming group -OR_6, or -OX where X is a pharmaceutically acceptable cation, or R_5 is -$N(R_7)_2$ where R_7 is H, or an aliphatic group of 1 to 10 carbon atoms, a cycloalkyl-$(CH_2)_n$- group of 4 to 10 carbons where n is 0-3 or both R_7 groups combine to form a ring having 4 to 6 carbons;

R_8 is hydrogen, C_1 to C_6 alkyl, or C_1 to C_6-acyl.

In another aspect, this invention covers pharmaceutical compositions containing the instant compounds and a pharmaceutically acceptable excipient.

Treatment of diseases related to or caused by leukotrienes, particularly LTB_4, or related pharmacologically active mediators at the end organ, are within the scope of this invention. This treatment can be effected by administering one or more of the compounds of formula I alone or in combination with a pharmaceutically acceptable excipient.

In yet another aspect, this invention relates to a method for making a compound of formula I, which method is illustrated in the Reaction Schemes given below and in the Examples set forth below.

DETAILED DESCRIPTION OF THE INVENTION

The following definitions are used in describing this invention and setting out what the inventors believe to be their invention herein.

"Aliphatic" is intended to include saturated and unsaturated radicals. This includes normal and branched chains, saturated or mono or poly unsaturated chains where both double and triple bonds may be present in any combination. The phrase "lower alkyl" means an alkyl group of 1 to 6 carbon atoms in any isomeric form, but particularly the normal or linear form. "Lower alkoxy" means the group lower alkyl-O-. "Acyl" means the radical having a terminal carbonyl carbon. "Halo" refers to and means fluoro, chloro, bromo or iodo. The phenyl ring may be substituted with one or more of these radicals. Multiple substituents may be the same or different, such as where there are three chloro groups, or a combination of chloro and alkyl groups and further where this latter combination may have different alkyl radicals in the chloro/alkyl pattern.

The phrase "a pharmaceutically acceptable ester-forming group" in R_2 and R_3 covers all esters which can be made from the acid function(s) which may be present in these compounds. The resultant esters will be ones which are acceptable in their application to a pharmaceutical use. By that it is meant that the mono or diesters will retain the biological activity of the parent compound and will not have an untoward or deleterious effect in their application and use in treating diseases. Such esters are, for example, those formed with one of the following radicals representing $-OR_6$ where R_6 is: C_1 to C_{10} alkyl, phenyl-C_1-C_6 alkyl, cycloalkyl, aryl, arylalkyl, alkylaryl, alkylarylalkyl, aminoalkyl, indanyl, pivaloyloxymethyl, acetoxymethyl, propionyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, or thienylglycyloxymethyl. Aryl includes phenyl and naphthyl, or heteroaromatic radicals like furyl, thienyl, imidazolyl, triazolyl or tetrazolyl. Most preferred ester-forming radicals are those where R_6 is alkyl, particularly alkyl of 1 to 10 carbons, [i.e. CH_3-$(CH_2)_n$- where n is 0-9], or phenyl-$(CH_2)_n$- where n is 0-4.

Pharmaceutically acceptable salts of the instant compounds are also intended to be covered by this invention. These salts will be ones which are acceptable in their application to a pharmaceutical use. By that it is meant that the salt will retain the biological activity

of the parent compound and the salt will not have untoward or deleterious effects in its application and use in treating diseases.

Pharmaceutically acceptable salts are prepared in a standard manner. The parent compound in a suitable solvent is reacted with an excess of an organic or inorganic acid, in the case of acid addition salts of a base moiety, or an excess of organic or inorganic base where R_4 is OH. Representative acids are hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, maleic acid, succinic acid or methanesulfonic acid. Cationic salts are readily prepared from alkali metal bases such as sodium, potassium, calcium, magnesium, zinc, copper or the like and ammonia. Organic bases include the mono or disubstituted amines, ethylene diamine, amino acids, caffiene, tromethamine, tris compounds, triethyl amine, piperazine and the like.

Oxides of the pyridyl ring nitrogen may be prepared by means known in the art and as illustrated herein. These are to be considered part of the invention.

If by some combination of substituents, a chiral center is created or another form of an isomeric center is created in a compound of this invention, all forms of such isomer(s) are intended to be covered herein. Compounds with a chiral center may be administered as a racemic mixture or the racemates may be separated and the individual enantiomer used alone.

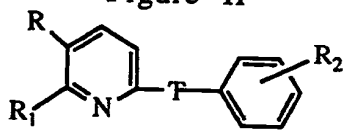
As leukotriene antagonists, these compounds can be used in treating a variety of diseases associated with or attributing their origin or affect to leukotrienes, particularly LTB_4. Thus it is expected that these compounds can be used to treat allergic diseases including those of a pulmonary and non-pulmonary nature. For example these compounds will be useful in antigen-induced anaphylaxis. They are useful in treating asthma and allergic rhinitis. Ocular diseases such as uveitis, and allergic conjunctivitis can also be treated by these compounds.

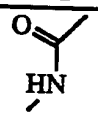
The preferred compounds of this invention are those where R is alkoxy, particularly alkoxy of 8 to 15 carbon atoms or substituted or unsubstituted phenyl-C_1 to C_{10}-aliphatic-O-; R_1 is -(C_1 to C_5 aliphatic)R_4 or -(C_1 to C_5 aliphatic)CH_2OR_8; and R_2 is COOH or an alkali metal salt thereof or $NHSO_2R_9$ where R_9 is $-CF_3$, C_1 to C_6 alkyl or phenyl. The more preferred compounds of this invention are those where R is alkoxy of 8 to 15 carbon atoms or alkoxy-substituted

phenyl-C_1 to C_8-alkenoxy or -C_1 to C_8-alkoxy; R_1 is -COR_5, -$CH_2CH_2COR_5$ or -CH=CH-COR_5; R_2 is -COOH or -$NHSO_2R_9$, particularly where R_9 is -CF_3; and R_3 is hydrogen or chloro.

The most preferred compounds are set out in Figure II.

Figure II



T	R	R_1	R_2
	$H_{21}C_{10}$	$HOOC(CH_2)_2$-	*m*-COOH
"	$H_{17}C_8$	HOOC-CH=CH-**	"
"	$H_{21}C_{10}$	"	"
"	$H_{25}C_{12}$	"	"
"	$H_{29}C_{14}$	"	"
"	p-MeO-Ph-$(CH_2)_8$-	"	"

* The carbonyl carbon is substituted on the pyridyl ring.
** Trans configuration.

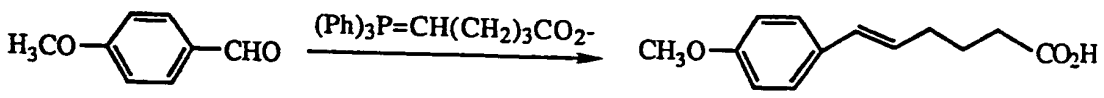
Synthesis

These compounds may be made by the intermediates and reagents as in the following reaction schemes. This specific set of intermediates is used to illustrate the general method. Scheme 1 illustrates a method for making compounds useful in making the R group. The other schemes use the materials whose preparation is described in scheme 1, or intermediates from commercial sources, to form the R group, then illustrate a method for making the compounds of formula I.

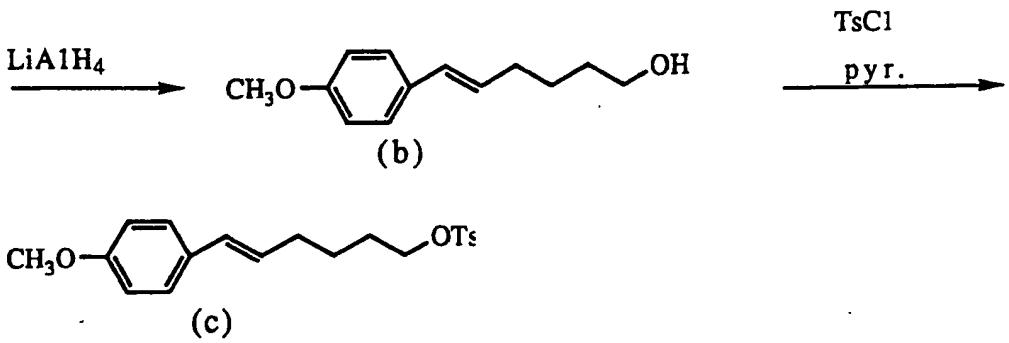
The R groups in formula I are available from chemical supply houses or can be made by one of the two methods outlined in Reaction Scheme I.

Scheme I(a) illustrates a method for making an unsaturated phenyl-alphatic R group.

Scheme 1(a)



(a)



While the methoxyphenyl compound is illustrated here, this series of steps and reagents may be used to make other substituted phenyl-ω-aliphatic groups denoted by R. The starting material, the benzaldehydes, are commercially available or can be readily made by known methods.

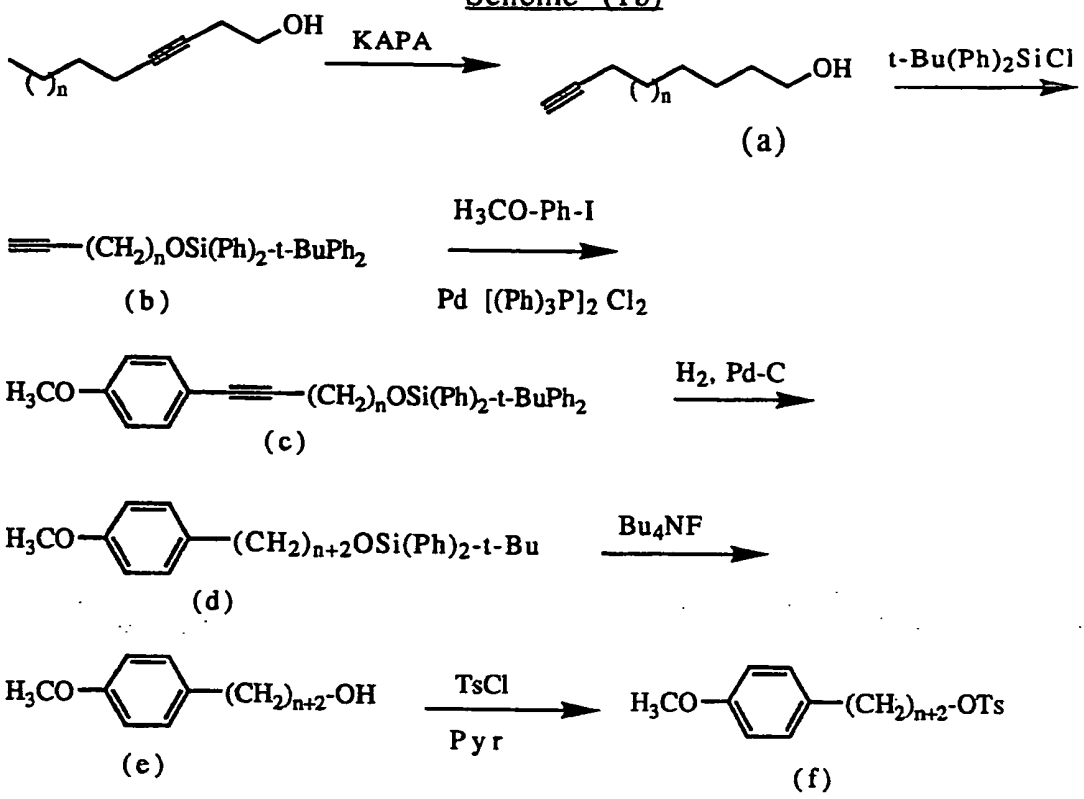
To make the acid (a), first an alkylsilazide is added to an inert solvent under an inert atmosphere. Then the phosphonium salt added. This addition can be done at room temperature or thereabouts. After a brief period of mixing, this mixture is usually a suspension, the benzaldehyde is added slowly at about room temperature. A slight molar excess of the phosphonium salt is employed. After an additional brief period of stirring at about room temperature, the reaction is quenched with water. The solution is acidified and the acid extracted with a suitable organic solvent. Further standard separatory and purification procedures may be employed as desired.

The alcohol is made by reducing the acid using a reducing agent. Lithium aluminum hydride or similar reducing agents may be employed and conditions may be varied as needed to effect the reduction.

The tosylate is prepared in an inert solvent employing p-toluene sulfonyl chloride and a base such as pyridine. Suitable conditions include carrying out the reaction at room temperature or thereabouts for a period of 1 to 5 hours. Other suitable leaving groups similar in function to the tosylate may be prepared and will be useful as a means for adding this R moiety to the pyridyl ring.

Reaction Scheme I(b) outlines one method for making an alkoxyphenylalkyl R group. This method could be used to make other R groups where phenyl is the ω group on the aliphatic chain, including substituted phenyl-containing groups.

Scheme (1b)



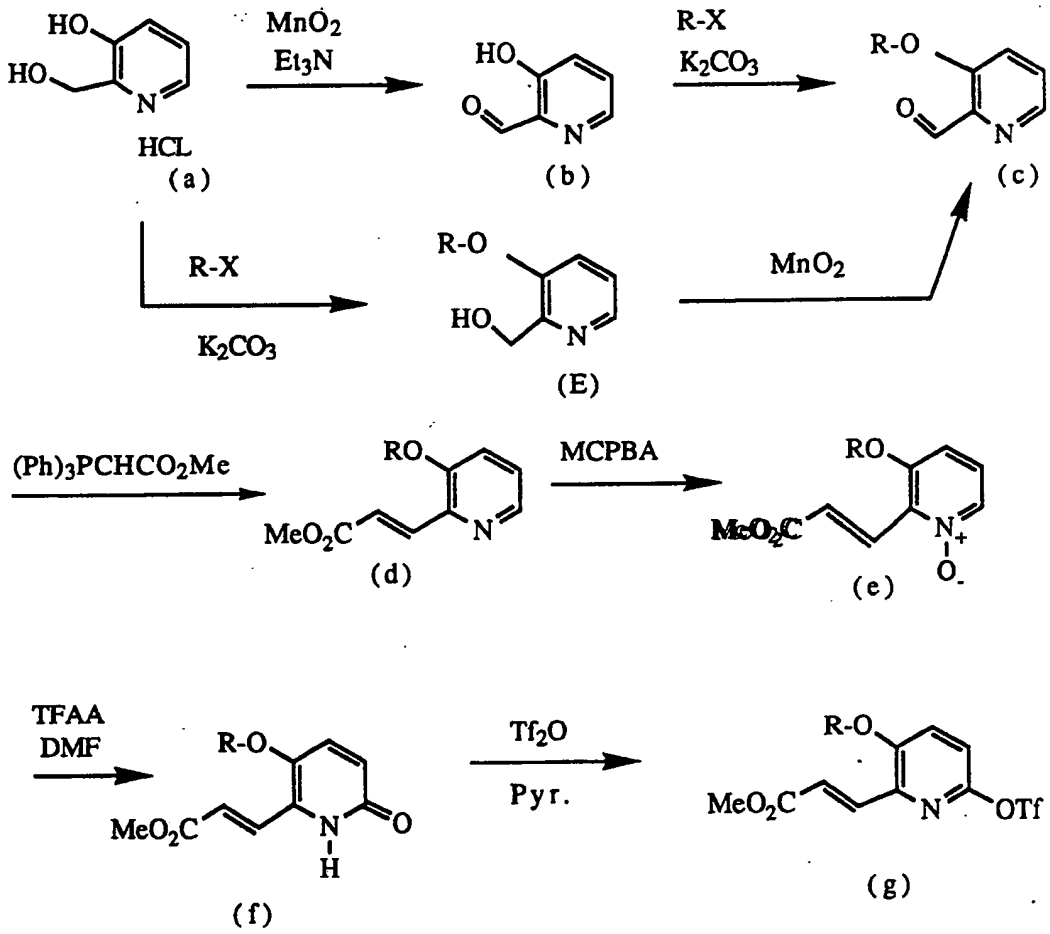
In those instances where an ω–yn-1-ol is not commercially available, it can be prepared from a corresponding 3-yn-1-ol by treating the alcohol with a strong base. Here an alkali metal amide was used. The alcohol is then protected in order to add the desired phenyl group at the terminal triple bond. A silyl ether was formed in this instance; it illustrates the general case. A halo-substituted-phenyl adduct is used to add the phenyl group at the triple bond. At this point, the triple bond can be reduced, most conveniently by catalytic means, eg. palladium-on-carbon and hydrogen. Alternatively, the triple bond could be retained and the intermediate carried on through as illustrated to the tosylate. The silyl group is removed and the resulting alcohol is converted to the tosylate, or another group which is sufficiently reactive so as to provide ready formation of an ether later in the synthesis of these compound.

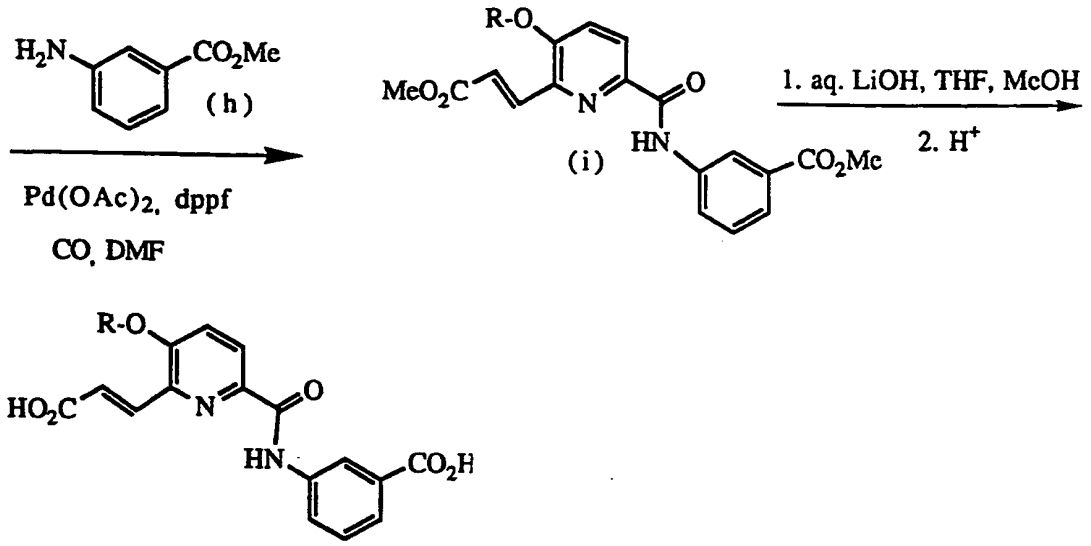
Using the compounds made in Scheme I and others purchased or prepared by known methods, in the following reaction schemes, one can prepare the compounds of formula I by following the sequence of reactions outlined in the following Schemes. Again, these schemes illustrate the general principle of how to make these compounds using specific examples. These schemes can be used to

make the other compounds disclosed herein by varying or modifying the chemistries illustrated here. Such variations or modifications will be changes in the reaction conditions, eg. temperature, pressure, length of reaction time, amount of reagents and the like. Reagents may be substituted for their equivalent or for a similar reagent which will effect the same or the equivalent product. Similarly, starting materials and intermediates may be varied to accomodate the need for making a particular compound.

One way of preparing compounds where the nitrogen of the amide linking group is on the phenyl ring is set out in Reaction Scheme 2.

Scheme 2





The foregoing scheme illustrates one synthetic route for making compounds of formula I where the carboxyl carbon is on the pyridyl ring. The 3-hydroxy-2-(hydroxymethyl)pyridine is commercially available or can be prepared by known, published means. This diol may be converted either to the aldehyde, then converted to the 3-alkoxy compound, or the 3-hydroxy group may be converted to the ether first, then the 2-position hydroxymethyl is oxidized to the aldehyde. Oxidizing the alcohol is readily accomplished using a mild oxidizing agent; manganese dioxide is preferred but other oxidizing agents could be successfully utilized in this step. Ethers are readily prepared from the corresponding α-halo-R group, or a compound such as a tosylate, under basic conditions.

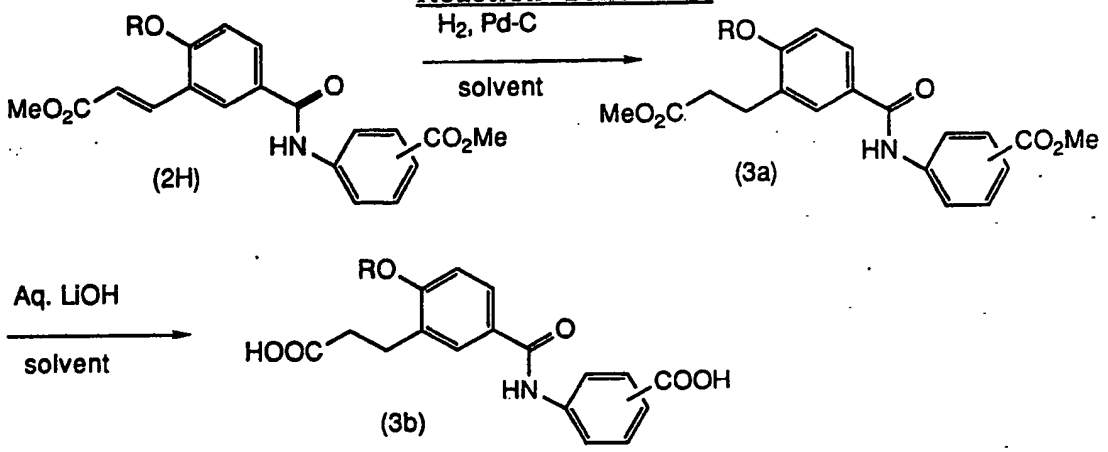
This 3-substituted-2-carboxyaldehyde (c) is then converted to the 2-carbomethoxyethenyl form (d) by means of the appropriate phosphoranylidene ester under conditions normally used for such a reaction. The resulting ester is then treated with a peroxy acid to make the N-oxide in preparation for making the pyridone (e). This step is illustrated by *m*-chloroperoxybenzoic acid, but other similar oxidizing agents could be used as well. Rearrangement of the N-oxide is then accomplished by means of trifluoroacetic anhydride or a similar reagent to produce the 2-pyridone (f).

Converting the 2-pyridone to the amide is accomplished by acylating the 2-pyridone (g) and then reacting this ester with the desired aminobenzoate (h) in the presence of certain catalysts and carbon monoxide. Trifluoromethanesulfonic anhydride illustrates the acylation step. The amidation reaction is effected by bubbling carbon

monoxide through a solution of the triflate in the presence of $Pd(OAc)_2$, 1,1'-bis(diphenylphosphino)ferrocene. The resulting diester (i) is then saponified using a mineral base to hydrolyze the ester groups. The resulting salt may be neutralized in order to recover the free acid. A free acid can be converted to another ester or made into the corresponding amide by known methods.

The saturated 3-position substituents are readily prepared from the alkene analog by catalytic hydrogenation. Reaction Scheme 3 illustrates this methodology.

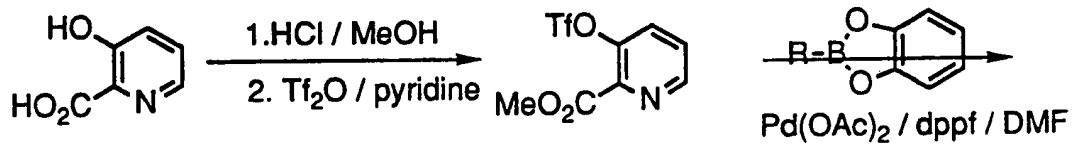
Reaction Scheme 3



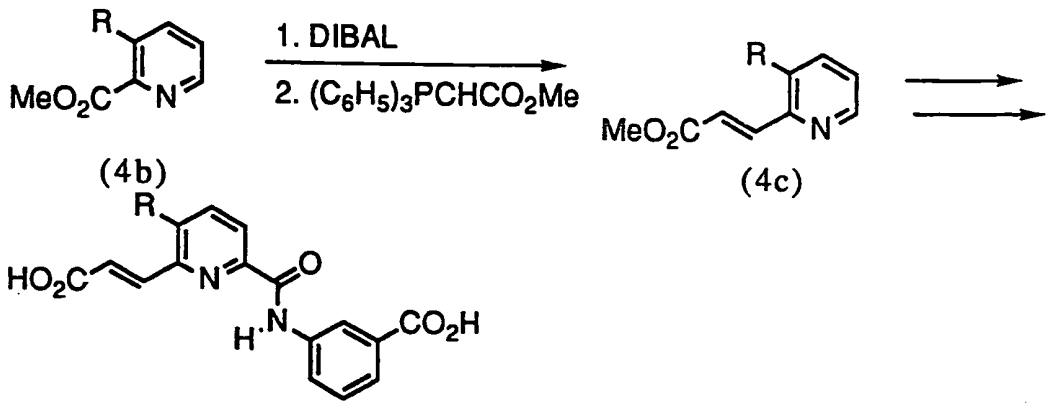
The diester is catalytically reduced (3a) by means of a heavy metal catalyst and hydrogen in a classic catalytic reduction reaction. Once the reduction is complete, a base can be used to hydrolyze the diester if the diacid (3b) is desired. Either compound can be converted to other compounds of this invention by the appropriate oxidation, reduction, esterification, amidation reaction, or by other means.

Carbon analogs of these compounds, that is those where the atom linking the R group to the 3-position is methylene, may be prepared by the sequence of steps set out in the fourth flow chart.

Scheme 4



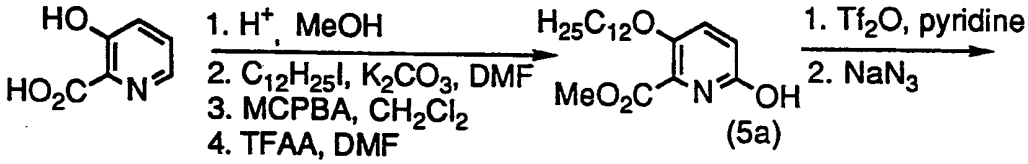
(4a)

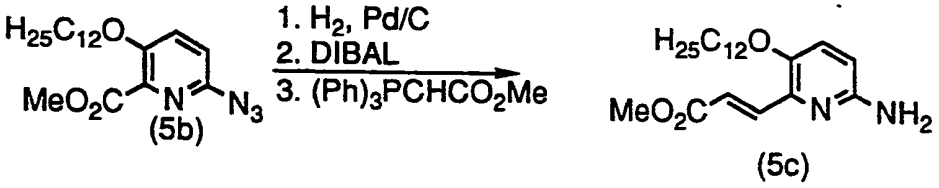


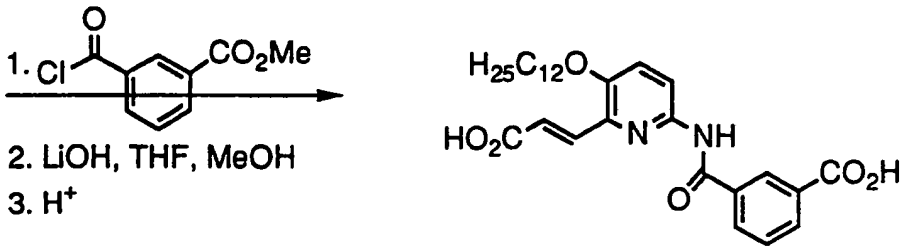
3-Hydroxypicolinic acid is converted to the alkyl ester by means of the corresponding alkanol and a acid catalyst. The hydroxyl group is converted to the trifluoromethanesulfonate (4a) using trifluoromethanesulfonic anhydride and pyridine. The lipid tail is then attached (4b) using the appropriate alkyl catechol boronate, prepared from 1-tridecene and catechol borane, using palladium coupling conditions ([Pd(OAc)2]. Then the alkyl ester is transformed into the corresponding aldehyde using an appropriate hydride, for example diisobtylaluminum hydride. This aldehyde is then subjected to a Wittig olefination, using for example, methyl(triphenyl-phosphoranylidene)acetate. The resulting pyridyl acrylate is then converted to the target compound via the same set of steps outlined in Scheme 2 above.

Reverse amides can be made by the sequence of steps given in Scheme 5.

Scheme 5







The commercially available 3-hydroxypicolinic acid is converted to an alkyl ester using an acid catalyst and the corresponding alkanol. This is followed by alkylation under standard conditions with, for example 1-idododecane or a similar 1-halo compound. This is best done using a weak base such as K_2CO_3 in dimethylformamide. This gives the 3-alkoxy derivative. Oxidizing the pyridine nitrogen and rearranging the resulting N-oxide provides the 2-pyridone. Oxidation is readily effected with a peroxy acid such as 3-chloroperoxybenzoic acid or similar oxidizing agent. The N-oxide (5a) rearrangement can be accomplished using trifluoroacetic anhydride in an appropriate solvent such as dimethylformamide.

Forming the trifluoromethanesulfonate is effected by means of trifluoromethanesulfonic anhydride and a base such as pyridine. Nucleophilic displacement with sodium azide gives the 2-azido pyridine derivative (5b). Reducing the azide to the amine is accomplished by catalytic hydrogenation. Reducing the alkyl ester to the aldehyde is done with a hydride, for example diisobutylaluminum hydride. A Wittig reaction is then used to make the 2-amino pyridine acrylate (5c). For example methyl(triphenylphosphoranylidene)-acetate may be used. Acylating the amine (methyl isophthalolyl chloride) followed by hydrolysis of the esters with base (LiOH, tetrahydrofuran, methanol) yields the target amide. These compounds can be further converted to an ester, amide, salt or similar compound as defined by formula I by means illustrated herein or generally known in the art.

Formulations

Pharmaceutical compositions of the present invention comprise a pharmaceutical carrier or diluent and some amount of a compound of the formula (I). The compound may be present in an amount to effect a physiological response, or it may be present in a lesser amount such that the user will need to take two or more units of the compositon to effect the treatment intended. These compositions may be made up as a solid, liquid or in a gaseous form. Or one of these

three forms may be transformed to another at the time of being administered such as when a solid is delivered by aerosol means, or when a liquid is delivered as a spray or aerosol.

The nature of the composition and the pharmaceutical carrier or diluent will, of course, depend upon the intended route of administration, for example parenterally, topically, orally or by inhalation.

For parenteral administration the pharmaceutical composition will be in the form of a sterile injectable liquid such as an ampule or an aqueous or non-aqueous liquid suspension.

For topical administration the pharmaceutical composition will be in the form of a cream, ointment, liniment, lotion, pastes, and drops suitable for administration to the eye, ear, or nose.

For oral administration the pharmaceutical composition will be in the form of a tablet, capsule, powder, pellet, atroche, lozenge, syrup, liquid, or emulsion.

When the pharmaceutical composition is employed in the form of a solution or suspension, examples of appropriate pharmaceutical carriers or diluents include: for aqueous systems, water; for non-aqueous systems, ethanol, glycerin, propylene glycol, corn oil, cottonseed oil, peanut oil, sesame oil, liquid parafins and mixtures thereof with water; for solid systems, lactose, kaolin and mannitol; and for aerosol systems, dichlorodifluoromethane, chlorotrifluoroethane and compressed carbon dioxide. Also, in addition to the pharmaceutical carrier or diluent, the instant compositions may include other ingredients such as stabilizers, antioxidants, preservatives, lubricants, suspending agents, viscosity modifiers and the like, provided that the additional ingredients do not have a detrimental effect on the therapeutic action of the instant compositions.

The pharmaceutical preparations thus described are made following the conventional techniques of the pharmaceutical chemist as appropriate to the desired end product.

In general, particularly for the prophylactic treatment of asthma, the compositions will be in a form suitable for administration by inhalation. Thus the compositions will comprise a suspension or solution of the active ingredient in water for administration by means of a conventional nebulizer. Alternatively the compositions will comprise a suspension or solution of the active ingredient in a

conventional liquified propellant or compressed gas to be administered from a pressurized aerosol container. The compositions may also comprise the solid active ingredient diluted with a solid diluent for administration from a powder inhalation device. In the above compositions, the amount of carrier or diluent will vary but preferably will be the major proportion of a suspension or solution of the active ingredient. When the diluent is a solid it may be present in lesser, equal or greater amounts than the solid active ingredient.

Usually a compound of formula I is administered to a subject in a composition comprising a nontoxic amount sufficient to produce an inhibition of the symptoms of a disease in which leukotrienes are a factor. When employed in this manner, the dosage of the composition is selected from the range of from 50 mg to 1000 mg of active ingredient for each administration. For convenience, equal doses will be administered 1 to 5 times daily with the daily dosage regimen being selected from about 50 mg to about 5000 mg.

Included within the scope of this disclosure is the method of treating a disease mediated by LTB_4 which comprises administering to a subject a therapeutically effective amount of a compound of formula I, preferably in the form of a pharmaceutical composition. For example, inhibiting the symptoms of an allergic response resulting from a mediator release by administration of an effective amount of a compound of formula I is included within the scope of this disclosure. The administration may be carried out in dosage units at suitable intervals or in single doses as needed. Usually this method will be practiced when relief of symptoms is specifically required. However, the method is also usefully carried out as continuous or prophylactic treatment. It is within the skill of the art to determine by routine experimentation the effective dosage to be administered from the dose range set forth above, taking into consideration such factors as the degree of severity of the condition or disease being treated, and so forth.

Pharmaceutical compositions and their method of use also include the combination of a compound of formula I with H_1 blockers where the combination contains sufficient amounts of both compounds to treat antigen-induced respiratory anaphylaxis or similar allergic reaction. Representative H_1 blockers useful here include: cromolyn sodium, compounds from the ethanolamines class (diphenhydramine), ethylenediamines (pyrilamine), the alkylamine

class (chlorpheniramine), the piperazine class (chlorcyclizine), and the phenothiazine class (promethazine). H_1 blockers such as 2-[4-(5-bromo-3-methylpyrid-2-yl)butylamino]-5-[(6-methylpyrid-3-yl)methyl]-4-pyrimidone are particularly useful in this invention.

Bioassays

The specificity of the antagonist activity of a number of the compounds of this invention is demonstrated by relatively low levels of antagonism toward agonists such as potassium chloride, carbachol, histamine and PGF_2.

The receptor binding affinity of the compounds used in the method of this invention is measured by the ability of the compounds to bind to [^{3}H]-LTB_4 binding sites on human U937 cell membranes. The LTB_4 antagonist activity of the compounds used in the method of this invention is measured by their ability to antagonize in a dose dependent manner the LTB_4 elicited calcium transient measured with fura-2, the fluorescent calcium probe. The methods employed were as follows:

U937 Cell Culture Conditions

U937 cells were obtained from Dr. John Bomalaski (Medical College of PA) and Dr. John Lee (SmithKline Beecham, Dept. of Immunology) and grown in RPMI-1640 medium supplemented with 10% (v/v) heat inactivated fetal calf serum, in a humidified environment of 5% CO_2, 95% air at 37°C. Cells were grown both in T-flasks and in Spinner culture. For differentiation of the U937 cells with DMSO to monocyte-like cells, the cells were seeded at a concentration of 1 x 10^5 cells/ml in the above medium with 1.3% DMSO and the incubation continued for 4 days. The cells were generally at a density of 0.75-1.25 x 10^6 cells/ml and were harvested by centrifugation at 800 x g for 10 min.

Preparation of U937 Cell Membrane Enriched Fraction

Harvested U937 cells were washed with 50 mM Tris-HCl, pH 7.4 at 25° C containing 1 mM EDTA (buffer A). Cells were resuspended in buffer A at a concentration of 5 x 10^7 cells/ml and disrupted by nitrogen cavitation with a Parr bomb at 750 psi for 10 min at 0° C. The broken cell preparation was centrifuged at 1,000 x g for 10 min. The supernatant was centrifuged at 50,000 x g for 30 min. The pellet was washed twice with buffer A. The pellet was resuspended at about 3 mg membrane protein/ml with 50mM Tris-HCl, pH 7.4 at 25°C and aliquots were rapidly frozen and stored at -70°C.

Binding of [^{3}H]-LTB_4 to U397 Membrane Receptors

[^{3}H]-LTB_4 binding assays were performed at 25° C, in 50 mM Tris-HCl (pH 7.5) buffer containing 10 mM $CaCl_2$, 10 mM $MgCl_2$, [^{3}H]-LTB_4, U937 cell membrane protein (standard conditions) in the presence or absence of varying concentrations of LTB_4, or SK&F compounds. Each experimental point represents the means of triplicate determinations. Total and non-specific binding of [^{3}H]-LTB_4 were determined in the absence or presence of 2 μM of unlabeled LTB_4, respectively. Specific binding was calculated as the difference between total and non-specific binding. The radioligand competition experiments were performed, under standard conditions, using approximately 0.2 μM [^{3}H]-LTB_4, 20-40 μg of U937 cell membrane protein, increasing concentrations of LTB_4 (0.1 nM to 10 nM) or other competing ligands (0.1 μM to 30 μM) in a reaction volume of 0.2 ml and incubated for 30 minutes at 25° C. The unbound radioligand and competing drugs were separated from the membrane bound ligand by a vacuum filtration technique. The membrance bound radioactivity on the filters was determined by liquid scintillation spectrometry.

Saturation binding experiments for U937 cells were performed, under standard conditions, using approximately 15-50 μg of U937 membrane protein and increasing concentrations of [^{3}H]-LTB_4 (0.02-2.0 mM) in a reaction volume of 0.2 ml and incubation at 22°C, for 30 minutes. LTB_4 (2 μM) was included in a separate set of incubation tubes to determine non-specific binding. The data from the saturation binding experiments was subjected to computer assisted non-linear least square curve fitting analysis and further analyzed by the method of Scatchard.

Uptake of Fura-2 by Differentiated U937 Cells

Harvested cells were resuspended at 2 x 10^6 cells/ml in Krebs Ringer Hensilet buffer containing 0.1% BSA (RIA grade), 1.1 mM $MgSO_4$, 1.0 mM $CaCl_2$ and 5 mM HEPES (pH 7.4, buffer B). The diacetomethoxy ester of fura-2 (fura-2/AM) was added to a final concentration of 2 nM and cells incubated in the dark for 30 minutes at 37° C. The cells were centrifuged at 800 x g for 10 minutes and resuspended at 2 x 10^6 cells/ml in fresh buffer B and incubated at 37°C for 20 minutes to allow for complete hydrolysis of entrapped ester. The cells were centrifuged at 800 x g for 10 minutes and resuspended in cold fresh buffer B at 5 x 10^6 cells/ml. Cells were

maintained on ice in the dark until used for fluorescent measurements.

Fluorescent Measurements-Calcium Mobilization

The fluorescence of fura-2-containing U937 cells was measured with a fluorometer designed by the Johnson Foundation Biomedical Instrumentation Group. Fluorometer is equipped with temperature control and a magnetic stirrer under the cuvette holder. The wave lengths are set at 339 nm for excitation and 499 nm for emission. All experiments were performed at 37°C with constant mixing.

U937 cells were diluted with fresh buffer to a concentration of 1 x 10^6 cells/ml and maintained in the dark on ice. Aliquots (2 ml) of the cell suspension were put into 4 ml cuvettes and the temperature brought up to 37°C, (maintained in 37°C, water bath for 10 min). Cuvettes were transferred to the fluorometer and fluorescence measured for about one minute before addition of stimulants or antagonists and followed for about 2 minutes post stimulus. Agonists and antagonists were added as 2 µl aliquots.

Antagonists were added first to the cells in the fluorometer in order to detect potential agonist activity. Then after about one minute 10 nM LTB_4 (a near maximal effective concentration) was added and the maximal Ca^{2+} mobilization $[Ca^{2+}]i$ was calculated using the following formula:

$$[Ca^{2+}]i = 224\left\{\frac{F\text{-}Fmin}{Fmax\text{-}F}\right\}$$

F was the maximum relative fluorescence measurement of the sample. *Fmax* was determined by lysing the cells with 10 µl of 10% Triton X-100 (final Concentration 0.02%). After *Fmax* was determined 67 µl of 100 mM EDTA solution (pH 10) was added to totally chelate the Ca^{2+} and quench the fura-2 signal and obtain the *Fmin*. The $[Ca^{2+}]i$ level for 10 nM LTB_4 in the absence of an antagonist was 100% and basal $[Ca^{2+}]i$ was 0%. The IC_{50} concentration is the concentration of antagonist which blocks 50% of the 10nM LTB_4 induced $[Ca^{2+}]i$ mobilization. The EC_{50} for LTB_4 induced increase in $[Ca^{2+}]i$ mobilization was the concentration for half maximal increase. The K_i for calcium mobilization was determined using the formula:

$$K_i = \frac{IC_{50}}{1+\frac{[LTB_4]}{[EC_{50}]}}$$

With the experiments described, the LTB_4 concentration was 10 nM and the EC_{50} was 2 nM.

Results of compounds tested by these methods are given in Figure III.

Figure III

	Binding, IC_{50}, (Ki), µM			Ca-Mobilization		
	U-937		PMN	U-937		PMN
Structure	Membrane	Whole Cell	Whole cell	IC_{50}, µM	% Agonist	% Agonist
Ex 1	4.0(1.4)	2.0	2.4	3.7	0	0
Ex 2	23(8.0)	4.7	-	3.0	0	0
Ex 3	47(17)	5.8	0.65	0.58	0	0
Ex 4	6.5(2.2)	3.4	2.2	8.5	0	0
Ex 5	41(14)	1.1	2.2	0.72	0	0
Ex 6*	6.1(2.0)	0.68	0.14	0.74	0	0

* Title compound.

Examples

The following set of examples are given to illustrate how to make and use the compounds of this invention. These Examples are just that, examples, and are not intended to circumscribe or otherwise limit the scope of this invention. Reference is made to the claims for defining what is reserved to the inventors by this document.

Example A

8-(4-Methoxyphenyl)octan-1-(4-toluenesulfonate)

A(1) 7-Octyn-1-ol

35% KH in mineral oil (27g, 240mmol) under an argon atmosphere was washed with hexane and treated dropwise with 1,3-diaminopropane. The mixture was stirred at room temperature until it became homogeneous. The flask was cooled to 0°C and 3-octyn-1-ol (10g, 79mmol, Lancaster Synthesis) was slowly added. The reaction was then stirred at room temperature for 18 hours. The reaction was quenched with H_2O (50mL) and the product was extracted into ether. The organic layer was washed with 10% HCl (3X15mL) and brine and dried ($MgSO_4$). Evaporation gave the title product which was used without further purification: ^1H NMR (90MHz, $CDCl_3$) δ 3.65 (t, J=5Hz, 2H, OCH_2), 2.23 (m, 2H, CH_2), 2.0 (m,

1H, acetylenic), 1.7-1.2 (m, 8H, $(CH_2)_4$); IR (neat) υmax 3350, 2930, 2125 cm^{-1}.

A(2) 7-Octyn-1-*t*-butyldiphenylsilyl ether.

7-Octyn-1-ol (3.8g, 30mmol) was dissolved in dimethylformamide (10mL) and treated with *t*-butylchlorodiphenylsilane (10.2mL, 33mmol) and imidazole (3.65g, 45mmol) at 0°C. The reaction was stirred at 0°C for 10 minutes and at room temperature for 3 hours. Water was added and the product was extracted into ethyl acetate. The ethyl acetate extract was washed with H_2O and brine and dried (Na_2SO_4). The solvent was evaporated and the residue purified by flash column chromatography (silica, hexanes) to give a yellow oil: ^1H NMR (250MHz, $CDCl_3$) δ 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 3.63 (t, 2H, OCH_2), 2.23 (m, 2H, CH_2), 1.97 (t, 1H, acetylenic), 1.6-1.3 (m, 8H, $(CH_2)_4$), 1.05 (s, 9H, *t*-butyl); IR (film) υmax 3321, 2940, 2125 cm^{-1}.

A(3) 8-(4-Methoxyphenyl)-7-octyn-1-*t*-butyldiphenylsilyl ether

To a flame-dried flask under an argon atmosphere was added 4-iodoanisole (5.34g, 22mmol) in triethylamine (50mL) followed by the addition of 7-octyn-1-t-butyldiphenylsilyl ether (9.84g, 27mmol), $(Ph_3P)_2PdCl_2$ (350mg, 0.44mmol), and CuI (200mg, 0.88mmol). The resulting mixture was heated at 50°C for 4 hours. Upon cooling to room temperature the reaction mixture was filtered and the solvent evaporated. The residue was partitioned between ethyl acetate and H_2O and the organic layer was collected and washed with brine and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by flash column chromatography (silica, 1% ethyl acetate in hexanes) to give an oil: ^1H NMR (250MHz, $CDCl_3$) δ 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 7.35 (d, 2H, aryl), 6.8 (d, 2H, aryl), 3.8 (s, 3H, OCH_3), 3.7 (t, 2H, OCH_2), 2.4 (t, 2H, CH_2), 1.7-1.3 (m, 8H, $(CH_2)_4$), 1.05 (s, 9H, *t*-butyl).

A(4) 8-(4-Methoxyphenyl)octan-1-t-butyldiphenylsilyl ether.

To 8-(4-methoxyphenyl)-7-octyn-1-t-butyldiphenylsilyl ether (2.2g, 4.6mmol) in ethanol (10mL) and ethyl acetate (10mL) was added 5% Pd/C (100mg). The mixture was subjected to 75 psi of H_2 for 4 hours. The reaction was filtered through Celite and the solvent evaporated to give an oil: ^1H NMR (250MHz, $CDCl_3$) δ 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 7.05 (d, 2H, aryl), 6.8 (d, 2H, aryl), 3.8 (s, 3H, OCH_3),

3.6 (t, 2H, OCH_2), 2.5 (t, 2H, benzylic), 1.75-1.3 (m, 12H, $(CH_2)_6$), 1.0 (s, 9H, *t*-butyl).

A(5) 8-(4-Methoxyphenyl)octan-1-ol.

8-(4-Methoxyphenyl)octan-1-t-butyldiphenylsilyl ether (2.2g, 4.6mmol) in tetrahydrofuran (20mL) was cooled to 0°C and treated with tetrabutylammonium fluoride (14mL, 14mmol, 1M in tetrahydrofuran). The cooling bath was removed and the reaction was stirred at room temperature for 24 hours. The reaction was diluted with ethyl acetate and was washed with H_2O and brine and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by flash column chromatography (silica, 0-20% ethyl acetate in hexanes) to give a white solid: m.p. 47-49°C; ^1H NMR (250MHz, $CDCl_3$) δ 7.15 (d, 2H, aryl), 6.86 (d, 2H, aryl), 3.85 (s, 3H, OCH_3), 3.68 (t, 2H, OCH_2), 2.62 (t, 2H, benzylic), 1.75-1.3 (m, 12H, $(CH_2)_6$).

A(6) 8-(4-Methoxyphenyl)octan-1-(4-toluenesulfonate).

6-(4-Methoxyphenyl)octan-1-ol (5.9g, 25mmol) was dissolved in dry CH_2Cl_2 (100mL) under an argon atmosphere and cooled to 0°C. To this was added pyridine (2.5mL, 30mmol) and 4-toluenesulfonyl chloride (5.4g, 28mmol). The reaction was stirred at 0°C for 20 minutes and at room temperature for 24 hours. The reaction solution was washed with H_2O and brine and dried (Na_2SO_4). The solvent was evaporated and the residue purified by flash column chromatography (silica, 0-10% ethyl acetate in hexanes) to give a white solid: ^1H NMR (250MHz, $CDCl_3$) δ 7.79 (d, 2H, aryl), 7.35 (d, 2H, aryl), 7.09 (d, 2H, aryl), 6.82 (d, 2H, aryl), 4.04 (s, 2H, OCH_2), 3.8 (s, 3H, OCH_3), 2.55 (t, 2H, benzylic), 2.46 (s, 3H, CH_3), 1.75-1.15 (m, 12H, $(CH_2)_6$).

Example B

6-(4-Methoxyphenyl)hexan-1-(4-toluenesulfonate)

B(1) 5-Hexyn-1-*t*-butyldiphenylsilyl ether

5-Hexyn-1-ol (3g, 30mmol, Aldrich) was dissolved in dimethylformamide (10mL) and treated with *t*-butylchlorodiphenylsilane (10.2mL, 33mmol) and imidazole (3.65g, 45mmol) at 0°C. The reaction was stirred at 0°C for 10 minutes and at room temperature for 3 hours. Water was added and the product

was extracted into ethyl acetate. The ethyl acetate extract was washed with H_2O and brine and dried (Na_2SO_4). The solvent was evaporated and the residue purified by flash column chromatography (silica, hexanes) to give a yellow oil: ^1H NMR (250MHz, $CDCl_3$) δ 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 3.65 (t, 2H, OCH_2), 2.2 (m, 2H, CH_2), 1.9 (t, 1H, acetylenic), 1.7 (m, 4H, CH_2-CH_2), 1.05 (s, 9H, *t*-butyl).

B(2) 6-(4-Methoxyphenyl)-5-hexyn-1-*t*-butyldiphenylsilyl ether.

To a flame-dried flask under an argon atmosphere was added 4-iodoanisole (5.34g, 22mmol) in triethylamine (50mL) followed by the addition of 5-hexyn-1-*t*-butyldiphenylsilyl ether (8.83g, 27mmol), $(Ph_3P)_2PdCl_2$ (350mg, 0.44mmol), and CuI (200mg, 0.88mmol). The resulting mixture was heated at 50°C for 4 hours. Upon cooling to room temperature the reaction mixture was filtered and the solvent evaporated. The residue was partitioned between ethyl acetate and H_2O and the organic layer was collected and washed with brine and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by flash column chromatography (silica, 1% ethyl acetate in hexanes) to give an oil: ^1H NMR (250MHz, $CDCl_3$) δ 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 7.35 (d, 2H, aryl), 6.8 (d, 2H, aryl), 3.8 (s, 3H, OCH_3), 3.7 (t, 2H, OCH_2), 2.4 (t, 2H, CH_2), 1.7 (m, 4H, CH_2-CH_2), 1.05 (s, 9H, *t*-butyl).

B(3) 6-(4-Methoxyphenyl)hexan-1-*t*-butyldiphenylsilyl ether.

To 6-(4-methoxyphenyl)-5-hexyn-1-*t*-butyldiphenylsilyl ether (2.0g, 4.6mmol) in ethanol (10mL) and ethyl acetate (10mL) was added 5% Pd/C (100mg). The mixture was subjected to 75 psi of H_2 for 4 hours. The reaction was filtered through Celite and the solvent evaporated to give an oil: ^1H NMR (250MHz, $CDCl_3$) δ 7.7 (d, 4H, aryl), 7.4 (m, 6H, aryl), 7.05 (d, 2H, aryl), 6.8 (d, 2H, aryl), 3.8 (s, 3H, OCH_3), 3.6 (t, 2H, OCH_2), 2.5 (t, 2H, benzylic), 1.55 (m, 4H, CH_2-CH_2), 1.3 (m, 4H, CH_2-CH_2), 1.0 (s, 9H, *t*-butyl).

B(4) 6-(4-Methoxyphenyl)hexan-1-ol.

6-(4-Methoxyphenyl)hexan-1-*t*-butyldiphenylsilyl ether (2.0g, 4.6mmol) in tetrahydrofuran (20mL) was cooled to 0°C and treated with tetrabutylammonium fluoride (14mL, 14mmol, 1M in tetrahydrofuran). The cooling bath was removed and the reaction was stirred at room temperature for 24 hours. The reaction was

diluted with ethyl acetate and was washed with H_2O and brine and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by flash column chromatography (silica, 0-20% ethyl acetate in hexanes) to give a white solid: ^1H NMR (250MHz, $CDCl_3$) δ 7.05 (d, 2H, aryl), 6.8 (d, 2H, aryl), 3.8 (s, 3H, OCH_3), 3.65 (t, 2H, OCH_2), 2.55 (t, 2H, benzylic), 1.6 (m, 4H, CH_2-CH_2), 1.4 (m, 4H, CH_2-CH_2).

B(5) 6-(4-Methoxyphenyl)hexan-1-(4-toluenesulfonate).

6-(4-Methoxyphenyl)hexan-1-ol (5.36g, 25mmol) was dissolved in dry CH_2Cl_2 (100mL) under an argon atmosphere and cooled to 0°C. To this was added pyridine (2.5mL, 30mmol) and 4-toluenesulfonyl chloride (5.4g, 28mmol). The reaction was stirred at 0°C for 20 minutes and at room temperature for 24 hours. The reaction solution was washed with H_2O and brine and dried (Na_2SO_4). The solvent was evaporated and the residue purified by flash column chromatography (silica, 0-10% ethyl acetate in hexanes) to give a white solid: ^1H NMR (250MHz, $CDCl_3$) δ 1.6-1.3 (m, 8H, $(CH_2)_4$), 2.4 (s, 3H, CH_3), 2.5 (t, 2H, benzylic), 3.8 (s, 3H, OCH_3), 4.0 (t, 2H, OCH_2), 6.80 (d, 2H, aryl), 7.0 (d, 2H, aryl), 7.3 (d, 2H, aryl), 7.8 (d, 2H, aryl).

Example C

E-6-(4-Methoxyphenyl)-1-(4-toluenesulfonate)-5-hexene

C(1) E-6-(4-Methoxyphenyl)-5-hexenoic acid.

To a freshly prepared solution of lithium hexamethyldisilazide (64mmol) in tetrahydrofuran (30mL), under an argon atmosphere, was added a suspension of (4-carboxybutyl)triphenylphosphonium bromide (17.6g, 30mmol) in tetrahydrofuran (45mL) at room temperature. The reaction was stirred for 15 minutes during which time the orange-red color of the ylide developed. A solution of 4-anisaldehyde (4.5g, 30mmol) in tetrahydrofuran (30mL) was added dropwise and stirring was continued for an additional 20 minutes. The reaction was quenched with H_2O (50mL) and diluted with ether (30mL). The aqueous layer was acidified to pH 1.0 with 3N HCl and the product was extracted into ethyl acetate (3X50mL). The combined organic layers were dried ($MgSO_4$) and the product was purified by flash column chromatography (silica, 1% methanol in CH_2Cl_2) to yield the E-olefin as a solid: ^1H NMR (200MHz, $CDCl_3$) δ 7.3

(d, 2H, aryl), 6.8 (d, 2H, aryl), 6.3 (d, 1H, olefin), 6.0 (m, 1H, olefin), 3.8 (s, 3H, OCH_3), 2.3 (m, 4H, allylic CH_2 and CH_2CO_2), 1.8 (q, 2H, CH_2).

C(2) E-6-(4-Methoxyphenyl)-5-hexen-1-ol.

E-6-(4-Methoxyphenyl)-5-hexenoic acid (1.1g, 5.0mmol) in dry ether (10mL) was slowly added to a suspension of $LiAlH_4$ (240mg, 6.0mmol) in ether (10mL) under an argon atmosphere. The reaction mixture was refluxed for 45 minutes. Upon cooling to room temperature the reaction was quenched with H_2O (10mL) followed by 6N H_2SO_4 (7mL). Ethyl acetate (20mL) was added and the organic layer was separated and dried ($MgSO_4$); evaporation gave a white crystalline solid: mp. 65-66°C; ^1H NMR (200MHz, $CDCl_3$) δ 7.2 (d, 2H, aryl), 6.8 (d, 2H, aryl), 6.3 (d, 1H, olefin), 6.1 (m, 1H, olefin), 3.8 (s, 3H, OCH_3), 3.6 (t, 2H, OCH_2), 2.2 (q, 2H, allylic), 1.5 (m, 4H, CH_2- CH_2); Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.65; H, 8.80, found: C, 75.45; H, 8.95; MS (CI): 207 (M+H).

C(3) E-6-(4-Methoxyphenyl)-1-(4-toluenesulfonate)-5-hexene.

E-6-(4-Methoxyphenyl)-5-hexen-1-ol (1.6g, 7.0mmol) was dissolved in dry CH_2Cl_2 (50mL) under an argon atmosphere and treated with 4-toluenesulfonyl chloride (7.0g, 36mmol) and pyridine (3mL). The reaction solution was stirred at room temperature for 3.5 hours. Water (40mL) was added to the reaction and the organic layer was separated and dried ($MgSO_4$). The product was purified by flash column chromatography (silica, 10% ethyl acetate in hexane) to give an oil: ^1H NMR (200MHz, $CDCl_3$) δ 7.8 (d, 2H, aryl), 7.3 (d, 2H, aryl), 7.2 (d, 2H, aryl), 6.8 (d, 2H, aryl), 6.2 (d, 1H, olefin), 6.0 (m, 1H, olefin), 4.1 (t, 2H, OCH_2), 3.8 (s, 3H, OCH_3), 2.4 (s, 3H, CH_3), 2.1 (q, 2H, allylic), 1.6 (m, 4H, CH_2- CH_2); MS (CI): 361 (M+H).

Example 1

N-(3-Carboxyphenyl)-6-(E-2-carboxyethenyl)-5-decyloxy-2-picolinamide, disodium salt

1(a) 3-Decyloxy-2-(hydroxymethyl)pyridine.

3-Hydroxy-2-(hydroxymethyl)pyridine hydrochloride (500mg, 3.09mmol, Aldrich, 85%) was dissolved in dry dimethylformamide (10mL) and treated sequentially with anhydrous K_2CO_3 (1.30g, 9.27mmol) and 1-iododecane (0.80mL, 3.71mmol). The reaction was

vigorously stirred under an argon atmosphere at 90°C for 1.5 hours. Upon cooling to room temperature the reaction mixture was diluted with ethyl acetate (100mL) and washed with H_2O (5X20mL) and brine and dried ($MgSO_4$). The compound was purified by flash column chromatography (silica, 20% ethyl acetate in petroleum ether) to give the captioned product: ^1H NMR (250MHz, $CDCl_3$) δ 8.17 (m, 1H, 6-pyridyl), 7.2 (m, 2H, 4-pyridyl, 5-pyridyl), 4.78 (s, 2H, CH_2), 4.48 (broad singlet, 1H, OH), 4.05 (t, J=6.6Hz, 2H, OCH_2), 1.9-0.90 (m, 19H, aliphatic).

1(b) 3-Decyloxy-2-pyridine carboxaldehyde.

3-Decyloxy-2-(hydroxymethyl)pyridine from 1(a), (560mg, 2.11mmol) in dry CH_2Cl_2 (7mL) was treated with MnO_2 (1.80g, 20.7mmol) and was stirred at room temperature for 24 hours. The reaction was filtered through a pad of Celite and the solvent was removed in vacuo giving the aldehyde as a pale yellow oil. The aldehyde was used directly in the next step without further purification.

1(c) 2-(E-2-Carboxymethylethenyl)-3-decyloxypyridine.

3- Decyloxy-2-pyridine carboxyaldehyde from the preceeding step (429mg, 1.63mmol) was dissolved in dry toluene (3.5mL) under an argon atmosphere and treated with methyl (triphenyl-phosphoranylidene)acetate (820mg, 2.45mmol). The reaction mixture was heated at 45°C, at which point the reaction became homogeneous, for 30 minutes. Upon cooling to room temperature the reaction was diluted with ethyl acetate (100mL) and washed with H_2O (2X20mL) and brine and dried ($MgSO_4$). The product was purified by flash column chromatography (silica, 10: 5: 85, ethyl acetate: CH_2Cl_2: petroleum ether) to give the product as a pale yellow solid: ^1H NMR (200MHz, $CDCl_3$) δ 8.25 (m, 1H, 6- pyridyl), 8.1 (d, J=16.2Hz, 1H, olefin), 7.25 (m, 2H, 4-pyridyl, 5-pyridyl), 7.05 (d, J=16.2Hz, 1H, olefin), 4.05 (t, J=6.6Hz, 2H, OCH_2), 3.85 (s, 3H, CO_2CH_3), 1.95-0.90 (m, 19H, aliphatic).

1(d) 2-(E-2-Carboxymethylethenyl)-3-decyloxypyridine N-oxide.

2-(E-2-Carboxymethylethenyl)-3-decyloxypyridine (390mg, 1.22mmol) was dissolved in dry CH_2Cl_2 (6mL) under an argon atmosphere, cooled to 0°C, and treated with 85%

3-chloroperoxybenzoic acid (278mg, 1.34mmol). Following the addition, the cooling bath was removed and the reaction was stirred at room temperature for 24 hours. The reaction solution was diluted with CH_2Cl_2 (50mL) and poured into saturated aqueous $NaHCO_3$ (50mL). The aqueous phase was extracted with CH_2Cl_2 (3X50mL) and the combined CH_2Cl_2 extracts were washed with brine and dried ($MgSO_4$). Flash column chromatography (silica, 10% CH_2Cl_2 in ethyl acetate) gave the N-oxide as a pale yellow solid: ^1H NMR (250MHz, $CDCl_3$) δ 8.18 (d, J=16.2Hz, 1H, olefin), 7.97 (d, J=6.5Hz, 1H, 6-pyridyl), 7.58 (d, J=16.2Hz, 1H, olefin), 7.11 (dd, J=8.6, 6.5 Hz, 1H, 5-pyridyl), 6.82 (d, J=8.6Hz, 1H, 4- pyridyl), 4.08 (t, J=6.6Hz, 2H, OCH_2), 3.82 (s, 3H, CO_2CH_3), 1.93- 0.88 (m, 19H, aliphatic).

1(e) 6-(E-2-Carboxymethylethenyl)-5-decyloxy-2-pyridone.

2-(E-2-Carboxymethylethenyl)-3-decyloxy-pyridine N-oxide (180mg, 0.537mmol) was dissolved in dry dimethylformamide (2.2mL) under an argon atmosphere and cooled to 0°C. To this was slowly added trifluoroacetic anhydride (0.76mL, 5.38mmol) followed by removal of the cooling bath. The reaction was stirred at room temperature for 18 hours. The reaction solution was diluted with ethyl acetate (75mL) and slowly poured into saturated aqueous $NaHCO_3$ (30mL). The organic layer was washed with $NaHCO_3$ (20mL) and brine and dried ($MgSO_4$). The product was obtained as a yellow solid and was used without further purification: ^1H NMR (250MHz, $CDCl_3$) δ 7.75 (d, J=16.3Hz, 1H, olefin), 7.40 (d, J=9.8Hz, 1H, 3-pyridyl), 7.01 (d, J=16.3Hz, 1H, olefin), 6.73 (d, J=9.8Hz, 1H, 4-pyridyl), 3.95 (t, J=6.6Hz, 2H, OCH_2), 3.82 (s, 3H, CO_2CH_3), 1.82-0.88 (m, 19H, aliphatic); MS (CI): 336 (M+H).

1(f) 6-(E-2-Carboxymethylethenyl)-5-decyloxy-2-trifluoro-methylsulfonate.

To a cooled (0°C) solution of 6-(E-2-carboxymethylethenyl)-5-decyloxy-2-pyridone (200mg, 0.596mmol) in dry CH_2Cl_2 (3.0mL) under an argon atmosphere was added dry pyridine (0.48mL, 5.96mmol) and trifluoromethanesulfonic anhydride (0.30mL, 1.78mmol). The reaction was stirred at 0°C for 15 minutes. The reaction was diluted with ethyl acetate (50mL) and washed with H_2O (20mL), 2% HCl (10mL), saturated $NaHCO_3$ (20mL), and brine and dried ($MgSO_4$). Purification by flash column chromatography (silica,

5% ethyl acetate in petroleum ether) gave the sulfonate as a colorless oil: ^1H NMR (250MHz, $CDCl_3$) δ 7.97 (d, J=15.8Hz, 1H, olefin), 7.36 (d, J=8.8Hz, 1H, 3-pyridyl), 7.11 (d, J=8.8Hz, 1H, 4-pyridyl), 6.96 (d, J=15.8Hz, 1H, olefin), 4.05 (t, J=6.5Hz, 2H, OCH_2), 3.83 (s, 3H, CO_2CH_3), 1.92-0.88 (m, 19H, aliphatic).

1(g) N-(3-Carboxymethylphenyl)-6-(E-2-carboxymethylethenyl)-5-decyloxy-2-picolinamide.

6-(E-2-Carboxymethylethenyl)-5-decyloxy-2-trifluoromethyl-sulfonate (160mg, 0.342mmol) was dissolved in dry dimethylformamide (1.25mL) and treated sequentially with methyl 3-aminobenzoate (775mg, 5.13mmol, Lancaster), $Pd(OAc)_2$ (4.5mg, 0.020mmol), and 1,1'-bis(diphenylphosphino)ferrocene (22mg, 0.040mmol). Carbon monoxide was gently bubbled through the solution for 5 minutes. The reaction was then heated at 90°C under a CO-atmosphere (balloon pressure) for 4 hours. Upon cooling to room temperature the reaction was diluted with ethyl acetate (75mL) and washed with 2% HCl (5X10mL), H_2O (15mL), saturated $NaHCO_3$ (15mL), and brine and dried ($MgSO_4$). Purification by flash column chromatography (silica, 10:20:70, ethyl acetate:CH_2Cl_2:petroleum ether) gave the amide as a colorless solid: ^1H NMR (250MHz, $CDCl_3$) δ 9.85 (s, 1H, NH), 8.29 (s, 1H, 2-phenyl), 8.27 (d, J=8.7Hz, 1H, 3-pyridyl), 8.14 (d, J=7.9Hz,1H, 4-phenyl), 8.10 (d, J=15.8Hz, 1H, olefin), 7.84 (d, J=7.9Hz, 1H, 6-phenyl), 7.48 (dd, J=7.9Hz, 1H, 5-phenyl), 7.38 (d, J=8.7Hz, 1H, 4-pyridyl), 7.08 (d, J=15.8Hz, 1H, olefin), 4.12 (t, J=6.6Hz, 2H, OCH_2), 3.95 (s, 3H, CO_2CH_3), 3.88 (s, 3H, CO_2CH_3), 1.96-0.88 (m, 19H, aliphatic); Anal. Calcd. for $C_{28}H_{36}O_6N_2$: C, 67.72; H, 7.31; N, 5.64, found: C, 67.50; H, 7.27; N, 5.57; MS (CI): 497.5 (M+H).

1(h) N-(3-Carboxyphenyl)-6-(E-2-carboxyethenyl)-5-decyloxy-2-picolinamide, disodium salt

N-(3-Carboxymethylphenyl)-6-(E-2-carboxymethylethenyl)-5-decyloxy-2-picolinamide (60mg, 0.121mmol) was dissolved in tetrahydrofuran (1.25mL) and MeOH (0.50mL) and treated with 1M LiOH (0.50mL). The reaction was stirred at room temperature for 6 hours. The reaction was made mildly acidic by the addition of 2% HCl (0.75mL), it was then diluted with ethyl acetate (50mL) and washed with H_2O (3X10mL) and brine and dried ($MgSO_4$); the solvent was removed in vacuo. The diacid was dissolved in saturated aqueous

Na_2CO_3 (3-5mL) and purified by Reversed Phase MPLC (RP-18 silica, 10-65% MeOH in H_2O) and isolated by lyophilization and was obtained as a white amorphous solid: ^1H NMR (250MHz, CD_3OD) δ 8.22 (s, 1H, 2-phenyl), 8.13 (d, J=8.7Hz, 1H, 3-pyridyl), 7.90-7.70 (m, 2H, 4-phenyl, 6- phenyl), 7.73 (d, J=15.8Hz, 1H, olefin), 7.65 (d, J=8.7Hz, 1H, 4- pyridyl), 7.48 (dd, J=7.9Hz, 1H, 5-phenyl), 7.17 (d, J=15.8Hz, 1H, olefin), 4.26 (t, J=6.6Hz, 2H, OCH_2), 1.98-0.82 (m, 19H, aliphatic); FAB-MS: (+ve), 513.1 (M+H); (-ve), 489.0 (M-Na).

Example 2
N-(3-Carboxyphenyl)-6-(2-carboxyethyl)-5-decyloxy-2-picolinamide

2(a) N-(3-Carboxymethylphenyl)-6-(2-carboxymethylethyl)-5-decyloxy-2-picolinamide.

N-(3-Carboxymethylphenyl)-6-(E-2-carboxymethylethenyl)-5-decyloxy-2-picolinamide (70mg, 0.141mmol) was dissolved in ethyl acetate (1mL), treated with 5% Pd/C (10mg), and stirred under an atmosphere of H_2 (balloon pressure) for 4 hours. The reaction could not be followed by TLC and the product was not soluble in ethyl acetate. The precipitated product was dissolved by the addition of CH_2Cl_2 (5mL) and the solution was filtered through a pad of Celite. The product was purified by flash column chromatography (silica, 5% ethyl acetate in CH_2Cl_2) to give captioned picolinamide as a white solid: ^1H NMR (250MHz, $CDCl_3$) δ 10.02 (s, 1H, NH), 8.48 (s, 1H, 2-phenyl), 8.18 (d, J=7.9Hz, 1H, 4-phenyl), 8.11 (d, J=8.5Hz, 1H, 3-pyridyl), 7.81 (d, J=7.9Hz, 1H, 6-phenyl), 7.46 (dd, J=7.9Hz, 1H, 5-phenyl), 7.20 (d, J=8.5Hz, 1H, 4-pyridyl), 4.05 (t, J=6.4Hz, 2H, OCH_2), 3.94 (s, 3H, CO_2CH_3), 3.68 (s, 3H, CO_2CH_3), 3.24 (t, J=6.9Hz, 2H, CH_2), 2.88 (t, J=6.9Hz, 2H, CH_2), 1.88-0.86 (m, 19H, aliphatic); Anal. Calcd. for $C_{28}H_{38}O_6N_2$: C, 67.45; H, 7.68; N, 5.62, found: C, 67.26; H, 7.76; N, 5.54; MS (CI): 499 (M+H).

2(b) N-(3-Carboxyphenyl)-6-(2-carboxyethyl)-5-decyloxy-2-picolinamide, dipotassium salt.

N-(3-Carboxymethylphenyl)-6-(2-carboxymethylethyl)-5-decyloxy-2-picolinamide (54mg, 0.108mmol) was suspended in tetrahydrofuran (1.1mL) and methanol (0.70mL) and treated with 1M LiOH (0.45mL, 0.45mmol). The reaction was stirred at room

temperature for 30 hours. The reaction mixture was diluted with ethyl acetate (50mL) and poured into 2% HCl (15mL). The ethyl acetate layer was washed with H_2O (3X20mL) and brine and dried ($MgSO_4$). The solvent was removed in vacuo and the solid diacid was dissolved in an aqueous $KHCO_3$ solution (3-5mL). Purification by Reversed Phase MPLC (RP-18 silica, 10-65% methanol in H_2O) and isolation by lyophilization gave the salt as a white amorphous solid: ^1H NMR (250MHz, CD_3OD) δ 8.49 (s, 1H, 2-phenyl), 8.00 (d, J=8.5Hz, 1H, 3-pyridyl), 7.88 (d, J=7.9Hz, 1H, 4-phenyl), 7.72 (d, J=7.9Hz, 1H, 6-phenyl), 7.36 (m, 2H, 4-pyridyl, 5-phenyl), 4.11 (t, J=6.4Hz, 2H, OCH_2), 3.19 (t, J=6.9Hz, 2H, CH_2), 2.66 (t, J=6.9Hz, 2H, CH_2), 1.92-0.87 (m, 19H, aliphatic); FAB-MS: (+ve), 547.4 (M+H); (-ve), 507.3 (M- K).

Example 3

N-(3-Carboxyphenyl)-6-(E-2-carboxyethenyl)-5-tetradecyloxy-2-picolinamide, dilithium salt

3(a) 3-Hydroxy-2-pyridine carboxyaldehyde.

3-Hydroxy-2-(hydroxymethyl)pyridine hydrochloride (1.32g, 6.9mmol, Aldrich, 85%) was dissolved in dry CH_2Cl_2 (35mL) and treated with triethylamine (1.1mL, 7.89mmol) and MnO_2 (6.0g, 69mmol). The reaction was stirred at room temperature for 18 hours, filtered through a pad of celite, and concentrated in vacuo. The crude aldehyde was used directly in the next step without further purification.

3(b) 3-Tetradecyloxy-2-pyridine carboxyaldehyde.

3-Hydroxy-2-pyridine carboxyaldehyde obtained above (appx. 6.9mmol) was dissolved in dry dimethylformamide (10mL) and treated sequentially with anhydrous K_2CO_3 (2.86g, 20.7mmol) and 1-iodotetradecane (2.00mL, 7.59mmol). The reaction was vigorously stirred under an argon atmosphere at 90°C for 4.5 hours. Upon cooling to room temperature the reaction mixture was diluted with ethyl acetate (100mL) and washed with H_2O (5X20mL) and brine and dried ($MgSO_4$). Purification by flash column chromatography (silica, 30% ethyl acetate in petroleum ether) gave the carboxyaldehyde as a pale yellow oil: ^1H NMR (250MHz, $CDCl_3$) δ 10.43 (s, 1H, CHO), 8.38

(dd, J=4.1, 1.5Hz, 1H, 6- pyridyl), 7.42 (m, 2H, 4-pyridyl, 5-pyridyl). 4.10 (t, J=6.5Hz, 2H, OCH_2), 1.91-0.88 (m, 27H, aliphatic).

3(c) 2-(E-2-Carboxymethylethenyl)-3-tetradecyloxypyridine.

Prepared according to the procedure described for 2-(E-2-carboxymethylethenyl)-3-decyloxypyridine: ^1H NMR (250MHz, $CDCl_3$) δ 8.22 (dd, J=4.0, 1.8Hz, 1H, 6-pyridyl), 8.10 (d, J=15.8Hz, 1H, olefin), 7.21 (m, 2H, 4-pyridyl, 5-pyridyl), 7.02 (d, J=15.8Hz, 1H, olefin), 4.02 (t, J=6.5Hz, 2H, OCH_2), 3.81 (s, 3H, CO_2CH_3), 1.88-0.88 (m, 27H, aliphatic).

3(d) 2-(E-2-Carboxymethylethenyl)-3-tetradecyloxypyridine N-oxide.

This compound was prepared according to the procedure described for 2-(E-2-carboxymethylethenyl)-3-decyloxypyridine N-oxide : ^1H NMR (250MHz, $CDCl_3$) δ 8.18 (d, J=16.2Hz, 1H, olefin), 7.95 (d, J=6.5Hz, 1H, 6-pyridyl), 7.58 (d, J=16.2Hz, 1H, olefin), 7.10 (dd, J=8.5, 6.5 Hz, 1H, 5-pyridyl), 6.80 (d, J=8.5Hz, 1H, 4-pyridyl), 4.08 (t, J=6.6Hz, 2H, OCH_2), 3.82 (s, 3H, CO_2CH_3), 1.88-0.88 (m, 27H, aliphatic).

3(e) 6-(E-2-Carboxymethylethenyl)-5-tetradecyloxy-2-pyridone.

This compound was prepared according to the procedure described for 6-(E-2-carboxymethylethenyl)-5-decyloxy-2-pyridone: ^1H NMR (250MHz, $CDCl_3$) δ 7.75 (d, J=16.3Hz, 1H, olefin), 7.40 (d, J=9.8Hz, 1H, 3-pyridyl), 7.01 (d, J=16.3Hz, 1H, olefin), 6.73 (d, J=9.8Hz, 1H, 4-pyridyl), 3.95 (t, J=6.6Hz, 2H, OCH_2), 3.82 (s, 3H, CO_2CH_3), 1.82-0.88 (m, 27H, aliphatic).

3(f) 6-(E-2-Carboxymethylethenyl)-5-tetradecyloxy-2-trifluoromethylsulfonate.

This compound was prepared according to the above procedure for preparing 6-(E-2-carboxymethylethenyl)-5-decyloxy-2-trifluoromethylsulfonate: ^1H NMR (250MHz, $CDCl_3$) δ 7.96 (d, J=15.7Hz, 1H, olefin), 7.35 (d, J=8.8Hz, 1H, 3-pyridyl), 7.10 (d, J=8.8Hz, 1H, 4-pyridyl), 6.96 (d, J=15.7Hz, 1H, olefin), 4.04 (t, J=6.5Hz, 2H, OCH_2), 3.82 (s, 3H, CO_2CH_3), 1.85-0.88 (m, 27H, aliphatic).

3(g) N-(3-Carboxymethylphenyl)-6-(E-2-carboxymethylethenyl)-5-tetradecyloxy-2-picolinamide.

The method of Example 1(g) was used to prepare N-(3-carboxymethylphenyl)-6-(E-2-carboxymethylethenyl)-5-decyloxy-2-picolinamide: ^{1}H NMR (250MHz, $CDCl_3$) δ 9.86 (s, 1H, NH), 8.29 (s, 1H, 2-phenyl), 8.27 (d, J=8.7Hz, 1H, 3-pyridyl), 8.13 (d, J=7.9Hz, 1H, 4-phenyl), 8.09 (d, J=15.8Hz, 1H, olefin), 7.84 (d, J=7.9Hz, 1H, 6-phenyl), 7.48 (dd, J=7.9Hz, 1H, 5-phenyl), 7.38 (d, J=8.7Hz, 1H, 4-pyridyl), 7.08 (d, J=15.8Hz, 1H, olefin), 4.12 (t, J=6.6Hz, 2H, OCH_2), 3.95 (s, 3H, CO_2CH_3), 3.88 (s, 3H, CO_2CH_3), 1.94-0.88 (m, 27H, aliphatic); MS (CI): 553.4 (M+H).

3(h) N-(3-Carboxyphenyl)-6-(E-2-carboxyethenyl)-5-tetradecyloxy-2-picolinamide, dilithium salt

N-(3-Carboxymethylphenyl)-6-(E-2-carboxymethylethenyl)-5-tetradecyloxy-2-picolinamide (173mg, 0.313mmol) was dissolved in tetrahydrofuran (4.0mL) and methanol (1.0mL) and treated with 1M LiOH (1.0mL). The reaction was stirred at room temperature for 48 hours. The resulting gel was dissolved in H_2O (3mL) and the tetrahydrofuran and methanol were removed in vacuo. The product was purified by Reversed Phase MPLC (RP-18 silica, 10-65% methanol in H_2O) and isolated by lyophilization to give the salt as a colorless amorphous solid: ^{1}H NMR (250MHz, CD_3OD) δ 8.32 (s, 1H, 2-phenyl), 8.12 (d, J=8.7Hz, 1H, 3-pyridyl), 7.85 (d, J=15.7Hz, 1H, olefin), 7.83 (d, J=7.9Hz, 1H, 4-phenyl), 7.76 (d, J=7.9Hz, 1H, 6-phenyl), 7.52 (d, J=8.7Hz, 1H, 4-pyridyl), 7.38 (dd, J=7.9Hz, 1H, 5-phenyl), 7.26 (d, J=15.7Hz, 1H, olefin), 4.16 (t, J=6.6Hz, 2H, OCH_2), 1.94-0.89 (m, 27H, aliphatic); FAB- MS: (+ve), 537 (M+H); (-ve), 529 (M-Li).

Example 4

N-(3-Carboxyphenyl)-6-(E-2-carboxyethenyl)-5-dodecyloxy-2-picolinamide, (dilithium salt)

N-(3-Carboxyphenyl)-6-(E-carboxyethenyl)-5-dodecyloxy-2-picolinamide, dilithium salt, was prepared according to the procedure described for N-(3-carboxyphenyl)-6-(E-carboxyethenyl)-5-tetradecyloxy-2-picolinamide, dilithium salt by substituting 1-iododododecane for 1-iodotetradecane (See Example 3).

4(a) 3-Dodecyloxy-2-pyridine carboxyaldehyde: ^1H NMR (250MHz, $CDCl_3$) δ 10.43 (s, 1H, CHO), 8.38 (dd, 1H, 6-pyridyl), 7.42 (m, 2H, 4-pyridyl, 5-pyridyl), 4.1 (t, 2H, OCH_2), 1.91-0.88 (m, 23H, aliphatic).

4(b) 2-(E-2-Carboxymethylethenyl)-3-dodecyloxypyridine: ^1H NMR (250MHz, $CDCl_3$) δ 8.22 (dd, 1H, 6-pyridyl), 8.1 (d, 1H, J=15.8Hz, olefin), 7.21 (m, 2H, 4-pyridyl, 5-pyridyl), 7.02 (d, 1H, J=15.8Hz, olefin), 4.02 (t, 2H, OCH_2), 3.81 (s, 3H, CO_2CH_3), 1.88- 0.88 (m, 23H, aliphatic).

4(c) 2-(E-2-Carboxymethylethenyl)-3-dodecyloxypyridine N-oxide: ^1H NMR (250MHz, $CDCl_3$) δ 8.15 (d, 1H, J =16.2Hz, olefin), 7.9 (d, 1H, 6-pyridyl), 7.58 (d, 1H, J=16.2Hz, olefin), 7.1 (dd, 1H, 5- pyridyl), 6.8 (d, 1H, 4-pyridyl), 4.08 (t, 2H, OCH_2), 3.82 (s, 3H, CO_2CH_3), 1.88-0.88 (m, 23H, aliphatic).

4(e) 6-(E-2-Carboxymethylethenyl)-5-dodecyloxy-2-pyridone: ^1H NMR (250MHz, $CDCl_3$) δ 8.0 (s, 1H, OH), 7.75 (d, 1H, J=16Hz, olefin), 7.4 (d, 1H, 3-pyridyl), 7.0 (d, 1H, J=16Hz, olefin), 6.7 (d, 1H, 4-pyridyl), 4.0 (t, 2H, OCH_2), 3.82 (s, 3H, CO_2CH_3), 1.85- 0.88 (m, 23H, aliphatic).

4(f) 6-(E-2-Carboxymethylethenyl)-5-dodecyloxy-2-trifluoro-methylsulfonate: ^1H NMR (250MHz, $CDCl_3$) δ 7.95 (d, 1H, J=15.9Hz, olefin), 7.37 (d, 1H, 3-pyridyl), 7.1 (d, 1H, 4- pyridyl), 6.95 (d, 1H, J=15.9Hz, olefin), 4.1 (t, 2H, OCH_2), 3.8 (s, 3H, CO_2CH_3), 1.89-0.88 (m, 23H, aliphatic).

4(g) N-(3-Carboxymethylphenyl]-6-(E-2-carboxymethylethenyl)-5-dodecyloxy-2-picolinamide: ^1H NMR (250MHz, $CDCl_3$) δ 9.86 (s, 1H, NH), 8.29 (s, 1H, aryl), 8.27 (d, 1H, 3-pyridyl), 8.13 (d, 1H, aryl), 8.09 (d, 1H, J=15.8Hz, olefin), 7.84 (d, 1H, aryl), 7.5 (t, 1H, aryl), 7.38 (d, 1H, 4-pyridyl), 7.08 (d, 1H, J=15.8Hz, olefin), 4.15 (t, 2H, OCH_2), 3.98 (s, 3H, CO_2CH_3), 3.88 (s, 3H, CO_2CH_3), 1.94-0.88 (m, 23H, aliphatic); Anal. Calcd. for $C_{30}H_{40}N_2O_6$: C, 68.68; H, 7.69; N, 5.34, found: C, 68.43; H, 7.54; N 5.21; MS (CI): 525 (M+H).

4(h) N-(3-Carboxyphenyl)-6-(E-2-carboxyethenyl)-5-dodecyloxy-2-picolinamide, dilithium salt: ^1H NMR (250MHz, CD_3OD) δ 8.37 (s, 1H, aryl), 8.12 (d, 1H, 3-pyridyl), 7.85 (d, 1H, J=15.7Hz, olefin), 7.83 (d,

1H, aryl), 7.77 (d, 1H, aryl), 7.55 (d, 1H, 4-pyridyl), 7.38 (t, 1H, aryl), 7.26 (d, 1H, J=15.7Hz, olefin), 4.16 (t, 2H, OCH_2), 1.90-0.88 (m, 23H, aliphatic); FAB- MS: (+ve), 509 (M+H); (-ve), 501 (M-Li).

Example 5

N-(3-Carboxyphenyl)-6-(E-2-carboxyethenyl)-5-octyloxy-2-picolinamide, dilithium salt

N-(3-Carboxyphenyl)-6-(E-carboxyethenyl)-5-octyloxy-2-picolinamide, dilithium salt , was prepared according to the procedure described for N-(3-carboxyphenyl)-6-(E-carboxyethenyl)-5-tetradecyloxy-2-picolinamide, dilithium salt (Example 3), substituting 1-iodooctane for 1-iodotetradecane.

5(a) 3-Octyloxy-2-pyridine carboxyaldehyde. ^1H NMR (250MHz, $CDCl_3$) δ 10.43 (s, 1H, CHO), 8.38 (dd, 1H, 6-pyridyl), 7.42 (m, 2H, 4-pyridyl, 5-pyridyl), 4.1 (t, 2H, OCH_2), 1.91-0.88 (m, 15H, aliphatic).

5(b) 2-(E-2-Carboxymethylethenyl)-3-octyloxypyridine. ^1H NMR (250MHz, $CDCl_3$) δ 8.22 (dd, 1H, 6-pyridyl), 8.1 (d, 1H, J=15.8Hz, olefin), 7.21 (m, 2H, 4-pyridyl, 5-pyridyl), 7.02 (d, 1H, J=15.8Hz, olefin), 4.02 (t, 2H, OCH_2), 3.81 (s, 3H, CO_2CH_3), 1.88- 0.88 (m, 15H, aliphatic).

5(c) 2-(E-2-Carboxymethylethenyl)-3-octyloxypyridine N-oxide. ^1H NMR (250MHz, $CDCl_3$) δ 8.15 (d, 1H, J=16.2Hz, olefin), 7.9 (d, 1H, 6-pyridyl), 7.58 (d, 1H, J=16.2Hz, olefin), 7.1 (dd, 1H, 5- pyridyl), 6.8 (d, 1H, 4-pyridyl), 4.08 (t, 2H, OCH_2), 3.82 (s, 3H, CO_2CH_3), 1.88-0.88 (m, 15H, aliphatic).

5(d) 6-(E-2-Carboxymethylethenyl)-5-octyloxy-2-pyridone. ^1H NMR (250MHz, $CDCl_3$) δ 8.0 (s, 1H, OH), 7.75 (d, 1H, J=16Hz, olefin), 7.4 (d, 1H, 3-pyridyl), 7.0 (d, 1H, J=16Hz, olefin), 6.7 (d, 1H, 4-pyridyl), 4.0 (t, 2H, OCH_2), 3.82 (s, 3H, CO_2CH_3), 1.85-0.88 (m, 15H, aliphatic).

5(e) 6-(E-2-Carboxymethylethenyl)-5-octyloxy-2-trifluoromethylsulfonate. ^1H NMR (250MHz, $CDCl_3$) δ 7.95 (d, 1H, J=15.9Hz, olefin), 7.37 (d, 1H, 3-pyridyl), 7.1 (d, 1H, 4-pyridyl), 6.95 (d, 1H, J=15.9Hz, olefin), 4.1 (t, 2H, OCH_2), 3.8 (s, 3H, CO_2CH_3), 1.89-0.88 (m, 15H, aliphatic).

5(f) N-(3-Carboxymethylphenyl)-6-(E-2-carboxymethylethenyl)-5-octyloxy-2-picolinamide. ^{1}H NMR (250MHz, $CDCl_3$) δ 9.86 (s, 1H, NH), 8.29 (s, 1H, aryl), 8.27 (d, 1H, 3-pyridyl), 8.13 (d, 1H, aryl), 8.09 (d, 1H, J=15.8Hz, olefin), 7.84 (d, 1H, aryl), 7.5 (t, 1H, aryl), 7.38 (d, 1H, 4-pyridyl), 7.08 (d, 1H, J=15.8Hz, olefin), 4.15 (t, 2H, OCH_2), 3.98 (s, 3H, CO_2CH_3), 3.88 (s, 3H, CO_2CH_3), 1.94-0.88 (m, 15H, aliphatic).

5(g) N-(3-Carboxyphenyl)-6-(E-2-carboxyethenyl)-5-octyloxy-2-picolinamide, dilithium salt ^{1}H NMR (250MHz, CD_3OD) δ 8.37 (s, 1H, aryl), 8.12 (d, 1H, 3-pyridyl), 7.85 (d, 1H, J=15.7Hz, olefin), 7.83 (d, 1H, aryl), 7.77 (d, 1H, aryl), 7.55 (d, 1H, 4-pyridyl), 7.38 (t, 1H, aryl), 7.26 (d, 1H, J=15.7Hz, olefin), 4.16 (t, 2H, OCH_2), 1.90-0.88 (m, 15H, aliphatic); FAB- MS: (+ve), 601.3 (M+H); (-ve), 598.9 (M-H).

Example 6

N-(3-Carboxyphenyl)-6-(E-2-carboxyethenyl)-5-[8-(4-methoxyphenyl)octyloxy]-2-picolinamide, dilithium salt

N-(3-Carboxyphenyl)-6-(E-2-carboxyethenyl)-5-[8-(4-methoxyphenyl)octyloxy]-2-picolinamide, dilithium salt was prepared according to the procedure described for N-(3-carboxyphenyl)-6-(E-2-carboxyethenyl)-5-tetradecyloxy-2-picolinamide, dilithium salt (Example 4), substituting 8-(4-methoxyphenyl)octan-1-(4-toluenesulfonate) for 1-iodotetradecane (See Example 3).

Following the procedures of Example 3(d) et seq, the following compounds were prepared.

6(a) 2-(E-2-Carboxymethylethenyl)-3-[8-(4-methoxyphenyl)-octyloxy]pyridine.

The tosylate of Example A was used to prepare this compound. ^{1}H NMR (250MHz, $CDCl_3$) δ 8.28 (dd, J=4.0, 1.8Hz, 1H, 6-pyridyl), 8.17 (d, J=15.8Hz, 1H, olefin), 7.28 (m, 2H, 4-pyridyl, 5-pyridyl), 7.12 (d, J=8.6Hz, 2H, aryl), 7.02 (d, J=15.8Hz, 1H, olefin), 6.89 (d, J=8.6Hz, 2H, aryl), 4.08 (t, J=6.5Hz, 2H, OCH_2), 3.87 (s, 3H, CO_2CH_3), 3.85 (s, 3H, OCH_3), 2.61 (t, J=7.5Hz, 2H, benzylic), 1.94-1.38 (m, 12H, aliphatic).

6(b) 2-(E-2-Carboxymethylethenyl)-3-[8-(4-methoxyphenyl)-octyloxylpyridine N-oxide.

^{1}H NMR (250MHz, $CDCl_3$) δ 8.02 (d, J=16.2Hz, 1H, olefin), 7.80 (d, J=6.5Hz, 1H, 6- pyridyl), 7.39 (d, J=16.2Hz, 1H, olefin), 7.00 (m, 2H, 5-pyridyl, 4-pyridyl), 6.85 (d, J=8.6Hz, 2H, aryl), 6.65 (d, J=8.6Hz, 2H, aryl), 3.91 (t, J=6.5Hz, 2H, OCH_2), 3.68 (s, 3H, CO_2CH_3), 3.62 (s, 3H, OCH_3), 2.37 (t, J=7.5Hz, 2H, benzylic), 1.82-1.10 (m, 12H, aliphatic).

6(c) 6-(E-2-Carboxymethylethenyl)-5-[8-(4-methoxyphenyl)-octyloxyl-2-pyridone.

^{1}H NMR (250MHz, $CDCl_3$) δ 7.75 (d, J=16.2Hz, 1H, olefin), 7.40 (d, J=9.8Hz, 1H, 3-pyridyl), 7.10 (d, J=8.6Hz, 2H, aryl), 7.00 (d, J=16.2Hz, 1H, olefin), 6.82 (d, J=8.6Hz, 2H, aryl), 6.70 (d, J=9.8Hz, 1H, 4-pyridyl), 3.95 (t, J=6.5Hz, 2H, OCH_2), 3.85 (s, 3H, CO_2CH_3), 3.82 (s, 3H, OCH_3), 2.57 (t, J=7.5Hz, 2H, benzylic), 1.85-1.22 (m, 12H, aliphatic).

6(d) N-(3-Carboxymethylphenyl)-6-(E-2-carboxymethylethenyl)-5-[8-(4-methoxyphenyl)octyloxyl-2-picolinamide.

Melting point - 70-73°C; ^{1}H NMR (250MHz, $CDCl_3$) δ 9.87 (s, 1H, NH), 8.31 (s, 1H, 2-phenyl), 8.28 (d, J=8.7Hz, 1H, 3-pyridyl), 8.15 (d, J=7.9Hz, 1H, 4-phenyl), 8.08 (d, J=15.8Hz, 1H, olefin), 7.85 (d, J=7.9Hz, 1H, 6-phenyl), 7.48 (dd, J=7.9Hz, 1H, 5-phenyl), 7.36 (d, J=8.7Hz, 1H, 4- pyridyl), 7.10 (d, J=8.6Hz, 2H, aryl), 7.08 (d, J=15.8Hz, 1H, olefin), 6.85 (d, J=8.6Hz, 2H, aryl), 4.12 (t, J=6.5Hz, 2H, OCH_2), 3.95 (s, 3H, CO_2CH_3), 3.88 (s, 3H, CO_2CH_3), 3.79 (s, 3H, OCH_3), 2.56 (t, J=7.5Hz, 2H, benzylic), 1.99-1.28 (m, 12H, aliphatic); Anal. Calcd. for $C_{33}H_{38}N_2O_7$: C, 68.97; H, 6.67; N, 4.88, found: C, 69.21; H, 6.88; N, 4.46; MS (CI): 575 (M+H).

6(e) N-(3-Carboxyphenyl)-6-(E-2-carboxyethenyl)-5-[8-(4-methoxyphenyl)octyloxyl-2-picolinamide, dilithium salt. Melting point 315°C (dec.); ^{1}H NMR (250MHz, CD_3OD) δ 8.31 (s, 1H, 2-phenyl), 8.12 (d, J=8.7Hz, 1H, 3-pyridyl), 7.86 (d, J=7.9Hz, 1H, 4-phenyl), 7.85 (d, J=15.8Hz, 1H, olefin), 7.76 (d, J=7.9Hz, 1H, 6-phenyl), 7.52 (d, J=8.7Hz, 1H, 4-pyridyl), 7.39 (dd, J=7.9Hz, 1H, 5-phenyl), 7.26 (d, J=15.8Hz, 1H, olefin), 7.07 (d, J=8.6Hz, 2H, aryl), 6.80 (d, J=8.6Hz, 2H, aryl), 4.15 (t, J=6.5Hz, 2H, OCH_2), 3.74 (s, 3H, OCH_3), 2.53 (t, J=7.5Hz, 2H, benzylic), 1.93-1.37 (m, 12H, aliphatic); Anal. Calcd. for

$C_{31}H_{32}N_2O_7Li_2 \cdot 5/2\ H_2O$: C, 61.69; H, 6.18; N, 4.64, found: C, 61.69; H, 5.91; N, 4.60; FAB-MS: (+ve), 559.4 (M+H); (-ve), 551.4 (M-Li).

Following the same procedure, but substituting for methyl 3-aminobenzoate the appropriate chloro substituted methyl 3-aminobenzoate, the following compounds were prepared:

N-(3-carboxy-6-chlorophenyl)-6-(E-2-carboxyethenyl)-5-[8-(4-methoxyphenyl)octyloxy]-2-picolinamide, dilithium salt; and

N-(3-carboxy-4-chlorophenyl)-6-(E-2-carboxyethenyl)-5-[8-(4-methoxyphenyl)octyloxy]-2-picolinamide, dilithium salt.

Example 7

Salts may be converted to the free acid by dissolving the salt in an aqueous solution and adding sufficient acid so as to bring the pH to about neutral (pH 7.0) or thereabouts. Any acid may be used though it is preferred to use a mineral acid such as HCl or the like. It is preferred to use a dilute rather than a concentrated acid, for example a 1 to 6 normal solution is most useful. Acid may be added at room temperature or thereabouts; no special conditions are required. Once the solution reaches a neutral pH or becomes acidic, the acid will precipitate out of solution an may be recovered by crystallization techniques, or any other technique which may prove useful for a given acid.

Example 8

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Inhalant Formulation

A compound of formula I, 1 to 10 mg/ml, is dissolved in isotonic saline and aerosilized from a nebulizer operating at an air flow adjustd to deliver the desired amount of drug per use.

Tablets: A compound of formula I, 1 to 10 mg/ml, is dissolved in isotonic saline and aerosolized from a nebulizer operating at an air flow adjusted to deliver the desired amount of drug per use.

Ingredients	Per Tablet	Per 10,000 Tablets
1. Active ingredient (Cpd of Form. I)	40 mg	400 g
2. Corn Starch	20 mg	200 g
3. Alginic acid	20 mg	200 g
4. Sodium alginate	20 mg	200 g
5. Magnesium stearate	1.3 mg	13 g
	101.3 mg	1013 g

Procedure for making tablets:

Step 1 Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2 Add sufficient water portionwise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3 The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4 The wet granules are then dried in an oven at (60°C) until dry.

Step 5 The dry granules are lubricated with ingredient No. 5.

Step 6 The lubricated granules are compressed on a suitable tablet press.

Suppositories:

Ingredients	Per Supp.	Per 1000 Supp.
1. Formula I compound Active ingredient	40.0 mg	40 g
2. Polyethylene Glycol 1000	1350.0 mg	1,350 g
3. polyethylene glycol 4000	450.0 mg	450 g
	1840.0 mg	1,840 g

Procedure:

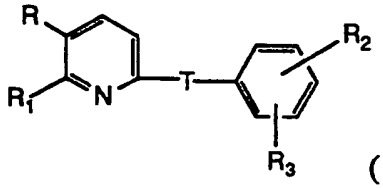
Step 1. Melt ingredient No. 2 and No. 3 together and stir until uniform.

Step 2. Dissolve ingredient No. 1 in the molten mass from Step 1 and stir until uniform.

Step 3. Pour the molten mass from Step 2 into supository moulds and chill and remove the suppositories from moulds and wrap.

What is claimed is:

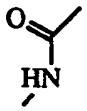
1. A compound of formula I



(I)

or a pharmaceutically acceptable salt or N-oxide thereof, where

T is the amide linking group



where the carbonyl carbon is bonded to the pyridyl ring;

R is C_1 to C_{20}-aliphatic, unsubstituted or substituted phenyl C_1 to C_{10}-aliphatic where substituted phenyl has one or more radicals selected from the group consisting of lower alkoxy, lower alkyl, trihalomethyl, or halo, or R is C_1 to C_{20}-aliphatic-O-, or R is unsubstituted or substituted phenyl C_1 to C_{10}-aliphatic-O- where substituted phenyl has one or more radicals which are lower alkoxy, lower alkyl, trihalomethyl, or halo;

R_1 is R_4, -(C_1 to C_5 aliphatic)R_4, -(C_1 to C_5 aliphatic)CHO, -(C_1 to C_5 aliphatic)CH_2OR_8, -CH_2OH or -CHO;

R_2 is hydrogen, -COR_5 where R_5 is -OH, a pharmaceutically acceptable ester-forming group -OR_6, or -OX where X is a pharmaceutically acceptable cation, or R_5 is -$N(R_7)_2$ where R_7 is H, or an aliphatic group of 1 to 10 carbon atoms, a cycloalkyl-$(CH_2)_n$- group of 4 to 10 carbons where n is 0-3 or both R_7 groups combine to form a ring having 4 to 6 carbons, or R_2 is $NHSO_2R_9$ where R_9 is -CF_3, C_1 to C_6 alkyl or phenyl;

R_3 is hydrogen, lower alkoxy, halo, -CN, COR_5, or OH;

R_4 is -COR_5 where R_5 is -OH, a pharmaceutically acceptable ester-forming group -OR_6, or -OX where X is a pharmaceutically acceptable cation, or R_5 is -$N(R_7)_2$ where R_7 is H, or an aliphatic group of 1 to 10 carbon atoms, a cycloalkyl-$(CH_2)_n$- group of 4 to 10 carbons where n is 0-3 or both R_7 groups combine to form a ring having 4 to 6 carbons;

R_8 is hydrogen, C_1 to C_6 alkyl, or C_1 to C_6-acyl.

2. A compound of claim 1 where R is C_1 to C_{20} aliphatic-O- or C_1 to C_{20} aliphatic, R_1 is -(C_1 to C_5 aliphatic)R_4 or -R_4, and R_2 is -COOH or a pharmaceutically acceptable salt thereof or -$NHSO_2R_9$.

3. A compound of claim 2 where R is C_8 to C_{15}-alkoxy and R_1 is -CH=CHR_4 where the double bond is cis or trans.

4. A compound of claim 3 where R is $H_{17}C_8$-O-, R_1 is trans -CH=CHCOOH, and R_2 is meta-substituted -COOH, the compound N-(3-carboxy-phenyl)-6-(E-2-carboxyethenyl)-5-octyloxy-2-picolinamide, its dilithium salt or another pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

5. A compound of claim 3 where R is $H_{21}C_{10}$-O-, R_1 is trans -CH=CHCOOH, and R_2 is meta-substituted -COOH, the compound N-(3-carboxy-phenyl)-6-(E-2-carboxyethenyl)-5-decyloxy-2-picolinamide, its disodium salt or another pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

6. A compound of claim 3 where R is $H_{25}C_{12}$-O-, R_1 is trans -CH=CHCOOH and R_2 is meta-substituted -COOH, the compound N-(3-carboxyphenyl)-6-(E-2-carboxyethenyl)-5-dodecyloxy-2-picolinamide, its dilithium salt or another pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

7. A compound of claim 3 where R is $H_{29}C_{14}$-O-, R_1 is trans -CH=CHCOOH, and R_2 is meta-substituted -COOH, the compound N-(3-carboxy-phenyl)-6-(E-2-carboxyethenyl)-5-tetradecyloxy-2-picolinamide, its dilithium salt or another pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

8. A compound of claim 2 where R is substituted or unsubstituted phenyl-C_1 to C_{10} aliphatic, R_1 is -(C_1 to C_5 aliphatic)R_4.

9. A compound of claim 8 where R is a lower alkoxy-substituted phenyl-C_1 to C_8-alkoxy group.

10. A compound of claim 9 where R is *p*-H_3C-O-phenyl-$(CH_2)_8$-O-, R_1 is HO_2CCH=CH-, and R_2 is meta-substituted -COOH, the compound N-(3-carboxyphenyl)-6-(E-2-carboxyethenyl)-5-[8-(4-methoxy-phenyl)octyloxy]-2-picolinamide, its dilithium salt or another pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

11. A compound of claim 2 where R_1 is $R_4CH_2CH_2$-.

12. A compound of claim 11 where R is $H_{21}C_{10}$-O-, R_1 is $HO_2CCH_2CH_2$- and R_2 is meta-substituted -COOH, the compound N-(3-carboxy-phenyl)-6-(2-carboxyethyl)-5-decyloxy-2-picolinamide,

N-(3-carboxy-6-chlorophenyl)-6-(E-2-carboxyethenyl)-5-[8-(4-methoxyphenyl)octyloxy]-2-picolinamide, N-(3-carboxy-4-chlorophenyl)-6-(E-2-carboxyethenyl)-5-[8-(4-methoxyphenyl)octyloxy]-2-picolinamide, a dilithium or dipotassium salt or another pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof.

13. A pharmaceutical composition comprising a pharmaceutical carrier or diluent and a compound of claim 1.

14. A pharmaceutical composition according to claim 13 in a form suitable for administration by inhalation, parenteral administration, or oral administration or topical administration.

15. A method of treating a pulmonary disease in which leukotrienes are a factor in a subject in need thereof comprising claim 1 alone or in combination with a pharmaceutically acceptable excipient.

16. The method of claim 15 where the disease is asthma.

17. The method of claim 16 which comprises administering a compound of claim 1 and an effective amount of an H_1 blocker.

18. A method of treating a non-pulmonary disease in which leukotrienes are a factor in a subject in need thereof comprising administration to such subject an effective amount of a compound of claim 1 alone or in combination with a pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/03940

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 213/81 A 61 K 31/44

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 213/00 A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	US,A,4555520 (R.N. MISRA et al.) 26 November 1985	

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
11-09-1991	21. 10. 91
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Mme. M. van der Drift

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers 15-18 because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1 (iv)

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest

[ ] No protest accompanied the payment of additional search fees

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9103940 SA 48456

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 26/09/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4555520	26-11-85	CA-A- 1264753	23-01-90
		DE-A- 3529628	27-02-86
		FR-A,B 2569192	21-02-86
		GB-A,B 2163428	26-02-86
		JP-A- 61057557	24-03-86